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SYPHILIS OF THE MITRAL VALVE AND MEMBRANOUS INTERVENTRICULAR SEPTUM OF THE HEART

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Submitted for publication May 29, 1935

When syphilitic lesions of the aortic valve are very extensive and the changes produced are extreme, it is not uncommon to find slight scarring along the edge of the mitral valve. Extensive syphilitic lesions of the mitral valve, however, have rarely been described. Staemmler (1) (2), reporting a case in 1930, was unable to find any examples in the literature, and up to the present time no other cases have been described. In his case, associated with aortic and mitral insufficiency, there were typical syphilitic lesions of the aorta and aortic valve. The lesions in the mitral valve involved the aortic or anterior segment. This portion of the valve was diffusely scarred from the point of its junction with the aortic valve to the free margin. Microscopical sections showed gummatous areas of necrosis surrounded by leucocytes, giant cells, and scar tissue. The lesions had apparently spread from the aorta and aortic valve directly to the great mitral leaf along the posterior or aortic surface. In view of the rare occurrence of these lesions the following two examples are described. In one of the cases, with rather fresh lesions, the changes in the mitral valve are practically identical with those reported by Staemmler.

Case 1. Unit No. 47419. History. A colored woman, 34 years old, entered the Johns Hopkins Hospital with evidence of heart failure and extreme aortic insufficiency three months after the onset of symptoms. There were also physical signs which suggested the presence of mitral insufficiency and possibly stenosis. For a period of two and a half months the signs and symptoms of heart failure increased and could not be relieved. First degree heart block developed. The liver became enlarged and tender. An extreme degree of oedema developed, and paracentesis was necessary. Death occurred five and a half months from the beginning of the present illness.

Examinations: The heart was somewhat enlarged on percussion. At the apex the first sound was muffled and followed by a low-pitched systolic murmur. The second sound was replaced by a blowing diastolic murmur. At the base of the heart, in the aortic area, a loud to-and-fro murmur was heard which obscured the normal sounds. *The pulse* was generally rapid and collapsing, varying from 80 to 140 beats per minute. All of the peripheral pulsations were exaggerated, and characteristic "pistol-shot" sounds were heard over the brachial and femoral arteries. *The blood pressure* varied between 150/0 and 160/25 millimetres of mercury. *The Blood:* Haemoglobin, 68 to 54 per cent. Red blood cells, 4,890,000 to 3,360,000 per cubic millimetre. *The blood Wassermann* was negative on two determinations, and positive (3+) on another. The patient's husband had a positive (4+) blood Wassermann reaction. *Temperature and Leucocytes:* Throughout the disease irregular unexplained fever and a leucocytosis (9,000 to 15,000 leucocytes per cubic millimetre) were present. *The urine* showed changes characteristic of chronic passive congestion.

Autopsy No. 13085: Anatomical Diagnosis: Extensive syphilis of the aorta, aortic valve, and membranous portion of the interventricular septum; gumma in body of mitral valve; extensive diffuse scarring of anterior segment of valve; localized scarring of mitral chordae tendineae; aortic and mitral insufficiency; cardiac dilatation, and slight hypertrophy; chronic passive congestion; necrosis of central liver cells; anasarca; chronic salpingitis; fibrous pelvic adhesions; localized scars in kidneys.

The body: There is a marked degree of generalized subcutaneous oedema, together with ascites and bilateral hydrothorax. *The heart* is larger than normal. It weighs 380 grams. The epicardial fat is atrophied. There are tough adhesions between the pericardium and the anterior surface of the ascending and transverse aorta. The right auricle and ventricle are dilated. In spite of marked dilatation the wall of the ventricle at the base is 5 millimetres thick. It is obviously hypertrophied. The foramen ovale and ductus arteriosus are closed. The valves on the right side are delicate and competent. The left auricle and ventricle are dilated. The wall of the ventricle, although dilated, is 14 millimetres thick at the base of the heart, and is slightly hypertrophied. No lesions that would suggest rheumatism are found in the wall of the left auricle. *The aorta and aortic valve* show typical syphilitic lesions, and the valve is insufficient. The changes are rather extreme, and extend in the aorta to a point approximately 1 cm. from the origin of the renal arteries. Beyond this point the aorta is normal except for a few delicate streaks of fat. The most marked aortic lesions are in the ascending and transverse arch where the wall is inelastic and very thick, measuring 5 to 6 mm. on section. The intima and adventitia are diffusely thickened, and macroscopic scars can be seen in the media. The intima is irregular, wrinkled and puckered, and has a pale white, translucent appearance. Practically no fat deposits can be seen. On the posterior wall of the ascending arch, 3 cm. above the valve, there is a thin area 1.5 cm. in diameter, marked externally by a slight bulge. A small haemorrhage has occurred beneath the intima in the center of this little

saccular dilatation. All the cusps of the aortic valve are shortened, measuring 7 mm. in height. They are diffusely thickened. The free edges are rolled and cord-like. The right and posterior cusps are separated from each other for a distance of 1.5 millimetres. The posterior cusp is attached to the aorta at a point 2 mm. lower than the attachment of the left cusp, and there is a gap of about 2 mm. between them. *The mitral valve and membranous interventricular septum:* The mitral valve is probably insufficient. The body of the great anterior or aortic segment of the valve is thick, stiff and leathery, varying from 2 to 3.5 mm. in thickness. The ventricular surface of this segment is wrinkled, puckered and rather translucent, like the inner surface of the syphilitic aorta. The membranous interventricular septum has a similar gross appearance, and the lesions in the mitral valve and septum are continuous with the lesions in the aortic cusps and aorta. The tip of the large posterior papillary muscle is scarred and partly calcified. Several of the chordae tendineae attached to it are fused together and shortened. The fused chordae, together with the tip of the scarred papillary muscle, form a firm, round, white cord, 16 mm. long and 4 mm. in diameter. It is attached at a point several millimetres behind the free edge of the thick anterior segment of the mitral valve and it seems unlikely that this cusp could have floated up into the normal position of closure. Along the line of the anterior mitral leaf there is some thickening of the valve, less marked, however, than above in the body of the valve. The posterior segment of the mitral valve shows slight localized areas of scarring along the line of closure, and a few of the attached chordae tendineae are also distinctly thickened but not appreciably shortened. *The other organs* show the effects of chronic passive congestion. There are dense pelvic adhesions binding the ovaries and Fallopian tubes together, and a few deep scars are found in each kidney.

Microscopical Lesions: Aorta: The lesions in the aorta are typical of syphilis. The adventitia is scarred. The vasa vasorum are surrounded by plasma cells, lymphocytes and monocytes. The intima of some of these vessels is thickened and the lumina are partly occluded by scar tissue. The usual vascular scars and perivascular inflammation are found in the media. The scars are numerous and some are large. The intima of the aorta has been converted into a thick layer of cellular connective tissue. The deeper layers are solid and dense. More superficially, the cells are larger and the fibers more loosely arranged. The syphilitic lesions at the root of the aorta are continuous with the lesions in the membranous septum, aortic leaflets, and mitral valve. *Aortic Valve:* The cusps are diffusely scarred. The scarring is especially marked along the free edges and where the valve joins the aorta. Blood vessels extend from the root of the aorta into the base of each scarred cusp and the vessels are surrounded by collections of mononuclear leucocytes. *Membranous Interventricular Septum:* The sections show lesions like those in the aorta and aortic valve, consisting of vascular scar tissue and perivascular round-cell inflammation. On the left ventricular surface of the septum there are stratified layers of scar tissue. The deeper strata are denser than the superficial layers. *Mitral Valve:* Between the two endocardial surfaces of the anterior segment of the valve there is an irregular, dense zone of vascular scar tissue continu-

ous with the scarred root of the aorta. Many of the blood vessels are surrounded by leukocytes, and in places the scarred valve shows dense patchy collections of lymphocytes and plasma cells. At one point, well above the line of closure of the valve, there is an area of caseous necrosis in this middle zone, surrounded by vascular granulation tissue and scar tissue which contains numerous lymphocytes and plasma cells. A few giant cells are found along the margin of the necrotic tissue. The ventricular surface of the thick mitral segment shows zones of scar tissue varying in density, and evidently laid down in successive layers. In the deeper layers there are blood vessels, often surrounded by leukocytes. The auricular surface of the valve is slightly thickened by a layer of loose connective tissue which overlies the original endocardial surface. Along the free edge of the valve there is slight diffuse scarring and the tissue is vascular. *The myocardium* shows a few hypertrophied fibers in the walls of the ventricles. Practically no scars are found, and there are no lesions to suggest rheumatism. In the posterior wall of the left auricle, directly above the insertion of the scarred mitral valve, numerous fine scars are found, together with perivascular round-cell inflammation. Similar localized changes are found in the muscular interventricular septum below the insertion of the scarred membranous portion of the septum. *Levaditi Stains:* No spirochaetes are found in the aorta or valves of the heart. The blocks of the valve, however, were fixed in Kaiserling's solution.

Case 2. R. J. History. A colored man, 56 years old, admitted to the Baltimore City Hospital on April 18th, 1934. For about one year he had been suffering from paroxysmal nocturnal dyspnoea, cough, and oedema of the ankles. For the next 7 months, while in the hospital, signs of cardiac decompensation and aortic insufficiency were present, and there was some clinical evidence of mitral insufficiency. The heart was large. There was a to-and-fro murmur over the aortic area, and a systolic murmur was heard both at the apex and in the aortic area The blood pressure varied from 150/85 to 210/70 millimetres of mercury. The blood Wassermann was positive. The patient died about one and a half years after the appearance of symptoms.

Autopsy No. 5891: Anatomical Diagnosis: Syphilis of the aorta (sinuses of Valsalva), aortic valve, membranous interventricular septum, and aortic segment of mitral valve; aortic and mitral insufficiency; scars in epicardium, endocardium, and myocardium; mural thrombus in right auricular appendage; cardiac hypertrophy and dilatation; chronic passive congestion; anasarca; coarse scars in liver; slight sclerosis of aorta and coronary arteries; moderate generalized sclerosis of small arteries; slight arteriolosclerosis; scar at apex of right lung; localized pelvic peritonitis (tuberculous).

The body is that of an oedematous and poorly nourished colored man with a decubitus ulcer over the left hip. The abdominal, pleural and pericardial cavities contain large quantities of fluid. In the pericardial sac there are 700 cc. of clear fluid. On the peritoneal surface, between the rectum and bladder, several small elevated white plaques are found about 2 mm. in diameter. The peritoneum about

them is reddened. Microscopically, they consist of localized areas of tuberculous peritonitis. No other active tuberculous lesions are found. *The heart and aorta:* The heart is elongated and very large, weighing 780 grams. Most of the epicardial fat has atrophied. On the surface of the right auricle are several small white patches of scar tissue. A number of depressed scars up to 2 or 3 mm. in diameter are found, covered by white plaques in the epicardium, scattered irregularly in the external wall of each ventricle. On section some of these scars are gray, while others are red and vascular. The right side of the heart is dilated and hypertrophied. The right auricular appendage contains a thrombus. The valves on the right side are delicate and competent. Below the pulmonary valve there is a star-shaped plaque of white scar tissue in the endocardium, about 1 cm. in diameter. The left auricle and ventricle are hypertrophied. There is some insufficiency of the aortic valve. The cusps are diffusely thickened from the sinuses of Valvalva upward. The free edge of each cusp forms a rolled, round, smooth cord, and there is some retraction of the cusps along the vertical lines of attachment of the commissures to the aorta. The intima of the aorta in the sinuses behind each cusp is thickened, white, and puckered in appearance. On section the adventitia is also thickened, and one can plainly see gross interruptions in the media. The lesions in the aorta do not extend beyond the sinuses of Valsalva. The membranous part of the interventricular septum and the anterior leaf of the mitral valve are very much thickened, opaque and leathery, and several of the chordae tendineae of the valve are somewhat thickened and are slightly shortened. The scarring extends downward from the aortic valve and membranous interventricular septum for a short distance to involve the endocardium over the muscular septum. The posterior segment of the mitral valve is delicate. *Other Lesions:* The coronary arteries show several thin sclerotic plaques which project slightly. The aorta beyond the valve is moderately sclerotic. The lungs are atelectatic. A small scar is found at the apex of the right lung. The liver and spleen show the effects of chronic passive congestion, and there are several deep, irregular scars extending from the surface of the liver, like old syphilitic lesions.

Microscopical Lesions: Aorta and Aortic Valve: At the root of the aorta, behind the valve, extensive typical syphilitic lesions are found. The adventitia is scarred. Many of the arterioles in the adventitia are nearly occluded by dense scar tissue in the intima, and some of these vessels are surrounded by lymphocytes and plasma cells. In the media of the root of the aorta many vascular scars are found, some showing round-cell perivascular inflammation. The media is especially scarred along the lines of attachment of the aortic commissures. Along these lines, too, the cusps of the valve are thickened by vascular scars showing round-cell infiltration. As the media of the aorta is traced towards its point of origin, the muscle is largely replaced by a series of very dense irregular hyaline scars which are separated from each other by thin loose scars. These contain vertically arranged blood vessels surrounded by lymphocytes and plasma cells. Above the scars in the media, especially in the angles formed by the junction of the aortic cusps with the aorta, the intimal tissue of the aorta is increased by irregular stratified layers of

scar tissue containing blood vessels, which are surrounded by leukocytes. This scar tissue in the intima of the aorta is continuous with similar vascular tissue laid down on the sinus surface of each cusp of the valve. The thickening of the aortic valve is produced chiefly by these layers of vascular scar tissue on the aortic surface of each cusp. *The Membranous Septum and Anterior Leaf of the Mitral Valve:* These structures are thickened by alternating large dense angular scars and looser vascular scars which can be traced directly downward into the membranous interventricular septum and into the middle zone of the anterior segment of the mitral valve from the root of the aorta. On the endocardial surfaces of the septum and mitral valve in the left ventricle, external to this central zone of vascular scar tissue, there are stratified scars running parallel to each other and varying in density. The auricular surface of the affected mitral leaf also shows a thin layer of scar tissue. Throughout the scarred portion of the valve and septum there is a patchy round-cell perivascular inflammation. No areas of recent necrosis are found, and Levaditi stains of tissue fixed in Kaiserling's solution show no spirochaetes. *The myocardium:* In the posterior wall of the left auricle near the insertion of the scarred mitral valve rather numerous scars are found together with perivascular round-cell inflammation. Similar lesions are present in the muscular interventricular septum beneath the scarred membranous portion. Many of the muscle fibers in the ventricles are hypertrophied, and throughout the ventricles there are irregularly scattered small scars. Some of the larger scars seen in the gross are associated with organizing thrombi in small branches of coronary arteries. There are no rheumatic lesions in the wall of the left auricle or in the myocardium of the ventricles. *Other Microscopical Lesions:* Most of the tissues show some effect of chronic passive congestion. Many of the central liver cells are necrotic and the sinusoids are distended. A few organizing thrombi are found in small pulmonary arteries. The small arteries in general are moderately sclerotic, and the terminal arterioles about the adrenal and in the spleen show marked hyaline sclerosis. Most of the arterioles in the kidney, however, are not appreciably altered.

SUMMARY

Two examples of syphilis of the mitral valve and membranous interventricular septum are described, occurring together with aortic insufficiency and typical syphilitic lesions of the aortic valve and aorta.

The lesions in the membranous septum and mitral valve are directly continuous with the syphilitic changes in the root of the aorta and aortic valves. The body of the anterior segment of the mitral valve is therefore chiefly affected, and the posterior mitral leaflet is relatively unaltered.

The gross lesions consist of diffuse leathery thickening of the membranous septum and great anterior mitral leaf. The left ventricular

surface of the affected mitral segment and septum may show wrinkling and puckering resembling typical gross syphilitic lesions of the aorta. The mitral chordae tendineae are slightly affected.

Microscopically, gummatous necroses or dense vascular scars with perivascular round-cell inflammation, or both, are found in the middle layers of the membranous septum and the mitral valve. These lesions, continuous with the syphilitic lesions in the media of the aorta, are overlaid by strata of scar tissue formed especially on the left ventricular surface of the valve and septum. Scars and perivascular inflammation are found in the wall of the left auricle and in the muscular interventricular septum near the insertion of the syphilitic mitral valve and membranous septum.

Mitral lesions were suspected clinically in both of the cases described. Each case was characterized by the presence of persistent cardiac decompensation which could not be relieved, lasting for five and a half months in one case with extreme aortic insufficiency, and for a year and a half in the other, in which the aortic valve was moderately insufficient. The anatomical changes in the mitral valve in each case suggested some degree of insufficiency, and it is probable that the mitral lesions were in part responsible for the degree and persistent character of the cardiac decompensation.

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(1) STAEMMLER: *Cntrlbl. f. allgem. Path. u. path. Anat.*, 1930, **48**, 177.
(2) *Idem:* Verhandl. der Deutschen path. Gesellschaft, 1930, **25**, 262.

EXPLANATION OF PLATES

(Photographs by Mr. Milton Kougl)

PLATE 1

FIG. 1. *Case 1.* One papillary muscle, the anterior mitral segment, and the membranous interventricular septum are thick, scarred and opaque, like the syphilitic aortic valve and aorta.

FIG. 2. *Case 1.* Microscopical section through the anterior segment of the mitral valve. In the center there is a casous area of necrosis in the body of the anterior leaf of the valve. Lymphocytes and a few giant cells surround this little gumma, which in turn is surrounded by vascular scar tissue.

Fig. 1.

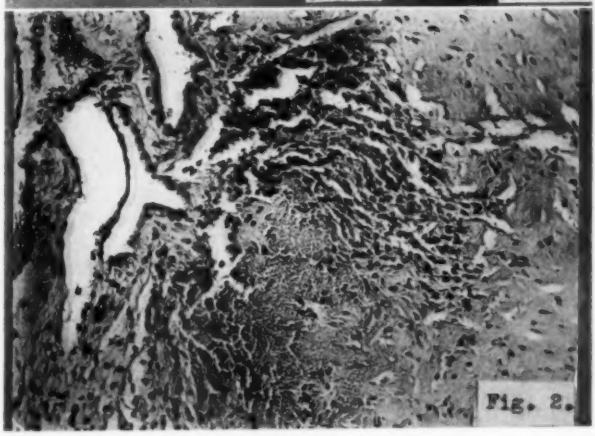

Fig. 2.

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PLATE 2

FIG. 3. *Case 2.* The aortic cusps, the membranous interventricular septum, and the anterior aortic segment are diffusely scarred, thick, and opaque. The edges of the aortic valve are rolled and cord-like. There is some displacement of the commissures.

FIG. 4. *Case 2.* Microscopical section through the anterior segment of the mitral valve. The photograph shows very dense, irregular masses of scar tissue, separated by thin, vertically arranged scars in which there are blood vessels and a few lymphocytes. Above these scars, on the endocardial surface, are stratified scars in which there are also blood vessels and a few leucocytes.

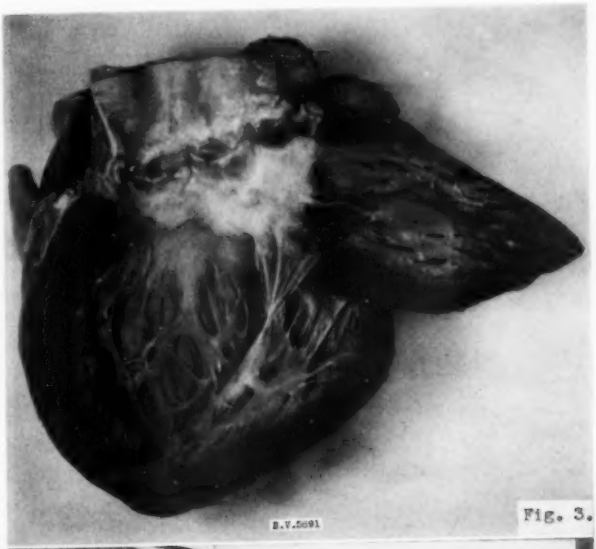

Fig. 3.

Fig. 4.

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THE HYPOPHYSIS CEREBRI OF THE FINBACK (BALAENOPTERA PHYSALUS) AND SPERM (PHYSETER MEGALOCEPHALUS) WHALE[1]

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Submitted for publication June 24, 1935

INTRODUCTION

The pituitary gland of the whale was chosen for special study because it offered promise of being suitable material for solving some of the important problems connected with this endocrine structure. One of these problems is the precise determination of the site of elaboration of the physiologically active components responsible for the multiple properties of extracts made from the posterior lobe (pars intermedia and pars nervosa). In other words, are these principles formed in the parts intermedia, in the pars nervosa, or in both?

This problem has been studied by many investigators who have tried to separate the pars intermedia from the pars nervosa and to

[1] Through a grant-in-aid from the National Research Council we were afforded the opportunity during the summer of 1934 of collecting pituitary glands of the finback whale (Balaenoptera physalus) and of the sperm whale (Physeter megalocephalus) at the whaling stations of the American Pacific Whaling Company at Rose Harbor and Naden Harbor, Queen Charlotte Islands, British Columbia, Canada. The paucity of our knowledge of the anatomy and physiology of this unique order of mammals, and the increasing difficulty of obtaining suitable material for study prompted us to collect, in addition to the hypophyses, a number of other organs and tissues. These were placed at the disposal of several investigators specially interested in the specimens, and their findings are published as separate contributions in this series of papers dealing with certain aspects of the biology of whales. One of these papers by Dr. W. L. Straus, Jr., entitled *Note on the Spinal Cord of the Finback Whale (Balaenoptera Physalus)* will shortly appear in the *Journal of Mammalogy*.

determine the activity of each of the separated parts. However, as is well known, the two portions of the posterior lobe in most mammals are very closely related and their intermingling is such that it is practically impossible to be certain that in any given case a complete separation has been effected. The conflicting results reported in the literature on such "pure" extracts bear out this statement amply. Furthermore, when a final accounting has been made of the properties which are resident in the pars nervosa and which are either completely or nearly absent from the pars intermedia, the temptation has been strong to ascribe to the glandular-like pars intermedia the site of origin of the precursor of these active substances. For these two reasons then it is highly desirable to study species of animals in which a pars intermedia is entirely absent, or in which the two parts are distinct, completely separable entities. One species fulfilling the former condition is the domestic fowl (Gallus domesticus) which has been studied by us. Our findings have been reported in abstract form (1), and a more detailed report is in the course of preparation.

Through the publications of Wislocki (1929) we were fortunate to learn that in the porpoise (Tursiops truncatus), the pars intermedia is absent. Our efforts to procure pituitaries from this species proved unsuccessful, because of the closing down of the porpoise fisheries at Cape Hatteras, where Wislocki secured his material. Thus far, we have not been able to find any other source of supply. We therefore turned our attention to other representatives of the Cetacea, among which are the whales.

A search of the literature,[2] as well as conversations with biologists who have made a special study of the whale, brought to light the fact that there was available no description of the whale's pituitary gland. This is not surprising when one visualizes the uninviting task of ob-

[2] While we were engaged in the study of the hypophyses which we collected during the summer of 1934, there appeared a short publication by Valsö (3) on the hormone content of the hypophysis of the blue whale (Balaenoptera sibbaldii). He reports that the anterior and posterior lobes of the pituitary of this whale are easily separable, and it appears from his sketch of the gland that there is no pars intermedia. He studied the anterior and posterior lobes for their gonadotrophic (follicle ripening and luteinizing effects) and intermedin (melanophore hormone) contents and concludes that all three of these hormones are formed in the anterior lobe.

taining the gland, which must be extricated from enormous masses of tissues, including thick muscle layers and a very dense skull.

With the aid of Dr. Remington Kellogg of the National Museum in Washington, D. C., the probable site of the gland was located from specimens of whale skulls. Arrangements were made with the American Pacific Whaling Company for us to spend some time at their whaling stations on the Queen Charlotte Islands, B. C. We were afforded the utmost coöperation by the officers and crews of the stations, and we wish to express to them our appreciation and thanks. Through their aid we were enabled to collect a number of pituitary glands from both the finback and the sperm whale.

STRUCTURE

The hypophyses of the finback and sperm whales greatly resemble that of the porpoise (Wislocki, 2) in gross structure and topographical relationships. In plate 1 is shown a life-size drawing of the hypophysis of a female finback whale, fifty-five feet in length. This illustration was made through the courtesy of Dr. G. L. Streeter, Director of the Carnegie Laboratory of Embryology, by the Institute's artist, Mr. James F. Didusch, whom we thank for the skilful manner in which he has reproduced the appearance of the structure. The gland lies in a shallow depression in the sphenoid bone, but a true sella turcica, as in other mammals, is not indicated, for, whereas the anterior clinoid processes are faintly prominent, the posterior clinoid processes are entirely absent. The gland is greatly flattened transversely and exhibits a very large anterior lobe (divisible into pars distalis and pars tuberalis) and a much smaller posterior lobe which is attached to the floor of the third ventricle by a thick stalk. A septum almost completely separates the two lobes which therefore are in contact only at the infundibulum. The hypophysis is so oriented that the anterior lobe alone lies adjacent to the bony floor, the posterior lobe thus being situated dorsal to the remainder of the gland. The total weight of the fresh gland ranges from 15 to 20 grams; it varies from 5 to 7 cm. in length, 3 to 4 cm. in width, and 1 to 2 cm. in thickness. A rich plexiform mat of blood vessels forming a thick rete mirabile imbedded in very tough, dense connective tissue closely encircles the gland.

Professor Wm. W. MacCallum has kindly made an histological study

of the hypophysis of a finback whale (Balaenoptera physalus) and his report is as follows.

Dr. MacCallum's Note on the Hypophysis of the Finback Whale (Balaenoptera physalus)

The hypophysis of the whale, as shown in plate 1, shows very distinctly a large mass which is the anterior lobe, and a much smaller mass which is the posterior lobe, extending into the stalk. The two are quite separate, as shown in a photograph of the median section. The posterior lobe is associated with a vascular mass which contains many large, thick-walled arteries. There is no gross indication of the existence of an intermediate zone.

Microscopically, the anterior lobe is quite homogeneous throughout. It is very vascular, the blood vessels running parallel with its broad surface. The actual gland tissue is in broad bands running between these vessels and is composed of cells which fall into three groups, of which two are far more abundantly represented than the third. The third group, composed of chromophobe cells, shows only a few such cells in each group and they are very inconspicuous. Definitely basophilic cells are very numerous in every strand of acinus; indeed, they seem more numerous than the second group which is made up of brilliant staining eosinophile cells. The nuclei in all these cells are vesicular with a distinct nucleolus. The basophilic cells are in general rather large, larger than the eosinophiles. The chromophobe cells tend to be ragged and small.

The posterior lobe is made up of a network of bands of fine fibrillar structure which take a purplish stain with pyrrol-blue and eosin. The blood vessels are rather numerous throughout it. It contains very few well defined nucleated cells. These seem to be related to the long, interwoven fibrils. They are cells with a very indistinct cytoplasm and apparently long fibrillary prolongations. A striking point is that scattered throughout the posterior lobe there are curious masses of granular material which takes a deep blue stain comparable to that of basophile cells. These are spoken of as masses because they are of all different sizes, from very minute groups of blue-stained granules to quite large rounded bodies with sharp outline. In the smaller groups the outline is sometimes quite sharp, often indistinct and irregular. It seems possible to see with very close inspection in some of them a faint outline resembling a nucleus, but this is very indistinct. It is quite as difficult to see anything resembling a nucleus in the larger ones although one larger one shows a sharp outline enclosing scattered basophilic granules within which there is a perfectly sharply outlined large nucleus-like mass which contains more compactly placed granules. In some places one has the impression that the granules from these bodies have been strewn free in the meshes of the tissues and one at least seems to be pouring out such granules, as though the wall had suddenly been broken. The significance of these masses is not clear.

Microscopically there is no suggestion of an intermediate zone, but as the material available was rather fragmentary it seems necessary to wait for represen-

tative serial sections from a specimen of hypophysis which is surely complete before arriving at a final conclusion.

Dr. MacCallum's description of the whale's hypophysis agrees well with that given by Wislocki for the pituitary of the porpoise, and also with Valsö's recent account of the same structure in the blue whale (Balaenoptera sibbaldi). It is thus obvious that the cetacean hypophysis is characterized by the absence of the pars intermedia both as a gross or as a microscopic entity.

Due to the fact, however, that the anterior lobe of the whale, like that of the chicken (1), exhibits frog melanophore expanding action, which is allocated to the pars intermedia of other mammals, it seems likely that in this animal the anterior lobe is not entirely homologous to the anterior lobe of other mammals. In most mammals, the buccal element of the hypophysis develops into two portions separated by Rathke's pouch. In the chicken it has been shown by Bruni (4) that with the early obliteration of Rathke's pouch there is a failure of the pars intermedia to develop as a separate structure from the buccal portion proper. Hence it forms a part of the anterior lobe in the chicken. It is probable that the absence of a pars intermedia as a distinct structure in the cetaceans is the result of a similar developmental process.

ACETONE-DESICCATED POWDER PREPARED FROM FRESH ANTERIOR AND POSTERIOR LOBES

For our pharmacological studies the two lobes were separated, cut in pieces and defatted and dehydrated by immersion in acetone. The material so obtained, which could now be ground into a fine powder, was kept in a desiccator, and served as the stock preparation from which extracts were made. The technique followed was that as outlined by Smith and McClosky (5) for the preparation of the international standard posterior pituitary powder from beef hypophyses. Dr. McClosky kindly furnished us with a quantity of the standard posterior pituitary powder (beef) which we used for preparing the standard solution (1 cc. contained 2 units) against which we assayed the extracts prepared from whale glands.

Unless otherwise stated, all our extracts contained 1 milligram of dry powder per 1 cc. and were made with 0.25 per cent acetic acid.

PHARMACOLOGICAL EXPERIMENTS WITH ANTERIOR AND POSTERIOR LOBE EXTRACTS

Our experiments were carried out chiefly for the purpose of ascertaining the specific distribution of the various pharmaco-dynamic activities present in our extracts. In brief, we found that the posterior lobe extracts of both the finback and sperm whales possessed pressor, antidiuretic and oxytocic activities, but did not produce expansion of the melanophore cells in frogs (Rana pipiens). We did, however, find that our anterior lobe extracts contained the melanophore hormone. This is in agreement with Valsö. We also found traces of pressor, antidiuretic and oxytocic action in the anterior lobe extracts, but these effects are undoubtedly due to contamination and do not represent true anterior lobe actions. The melanophore hormone is present in the so-called posterior lobe extracts prepared from beef hypophyses, and is now generally conceded to be formed by the cells of the pars intermedia. Further direct proof of this has been obtained by tissue culture experiments carried out with Mrs. M. R. Lewis in the Carnegie Laboratory of Embryology. These experiments will be reported in another communication.

EFFECTS OF EXTRACTS ON BLOOD PRESSURE

Blood pressure measurements were carried out by the usual manometric method on cats under luminal and on chickens under urethane anesthesia.

From tracings 1, 2, 3, and 4 in figure 1 it can be readily seen that in cats the responses elicited by extracts (prepared from the desiccated powders) of dog, sperm whale, beef, and finback whale posterior pituitaries are of the same order of magnitude, indicating that the glands from these species have similar quantities of the pressor component per unit of weight. Repeated injections of these extracts produce a markedly lessened effect, and tolerance is readily established. In addition the pressor component is readily destroyed by alkali treatment. Anterior lobe extracts (tracing 5), injected in three times the concentration, give a very small blood pressure rise which does not occur after alkali treatment; this effect is probably due to posterior lobe contamination, which is difficult to avoid under the conditions

under which the glands were collected. Extracts of the posterior lobes of chickens prepared from fresh glands also have pressor activity comparable with that of the standard preparation (tracings 6 and 7).

In figure 2 are shown the blood pressure changes after injections of

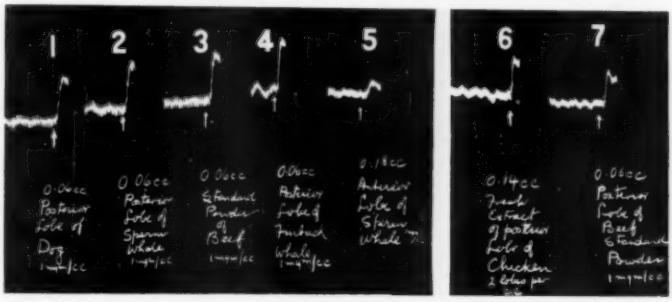

FIG. 1. BLOOD PRESSURE TRACINGS OF CAT

Wt. 3.46 kg. Luminal anesthesia. Injections were made intravenously at half-hour intervals.

FIG. 2. BLOOD PRESSURE TRACINGS TAKEN FROM FEMORAL ARTERY OF CHICKENS ANESTHETIZED WITH URETHANE

Tracings 1, 2 and 3 were obtained from a chicken weighing 0.85 kg., and tracings 4, 5 and 6 from another chicken, wt. 1.4 kg. Injections were made at half-hourly intervals.

the different extracts into anesthetized chickens. It will be noted that the standard and dog extracts gave the expected depressor response, while both whale extracts caused an initial depressor action, followed promptly by a sustained rise. We interpret this to mean that in the whale posterior lobe there is a disproportion in the amounts of

pressor and oxytocic components, for it is now believed that the oxytocic principle is responsible for the fall in pressure in the chicken and this is the predominant effect when equivalent quantities of the pressor and the oxytocic principles (ordinary pituitary extract) are injected (6, 7). The pressor principle causes mainly a rise of pressure, and when it is present in greater amount than the oxytocic principle, one obtains a mixed effect such as is exhibited by the whale posterior lobe extracts.

That our interpretation is correct is borne out by the oxytocic assays which are reported below.

THE ANTIDIURETIC EFFECTS

It is generally recognized that the pressor and antidiuretic actions of posterior pituitary extracts are elicited by the same principle. We measured the antidiuretic effects of our extracts according to a modification of Burn's technique (8), which is an adaptation of Gibbs' method (9). Two sets of sixteen rats of uniform age and weight were used in these experiments. Each set was divided into four groups of four animals. Food was withheld for about 24 hours, but water was removed from the cage only half an hour before the beginning of the experiment. Instead of giving tap water by stomach tube, as Burn did, we injected 10 cc. of tap water at 37°C. intraperitoneally into each animal and immediately thereafter administered subcutaneously 0.5 cc. of the diluted extract (0.25 cc. of extract, 1 mgm. per cc., diluted to 5 cc. with saline). In table 1 are given the results of one set of experiments with anterior and posterior lobe extracts of the finback whale. Essentially similar results were obtained with sperm whale extracts. We tested the extracts of each species of whale on both sets of rats. The data demonstrate clearly that the whale posterior lobe extracts possess a degree of antidiuretic activity comparable with or even greater than that of the standard preparation.

THE OXYTOCIC ACTIVITY

We estimated the oxytocic activity of the extracts by means of the standard technique employing uteri of virgin guinea-pigs. We found that the oxytocic activity is vested in the posterior lobe extracts, but we were forcibly struck by the fact that this action was con-

siderably less than that found in the standard beef extract. This unique fact seemed to us to be of such significance as to warrant careful verification and extensive investigation. We accordingly enlisted the coöperation of Dr. Wm. T. McClosky of the Pharmacological Laboratory, U. S. Department of Agriculture, Washington, D. C., who has had a very wide experience in the assay of posterior pituitary preparations, and we have planned to carry out a somewhat elaborate analysis of these extracts, as well as preparations of pituitary glands from other species of animals. Suffice it to say for the present that the oxytocic activity of finback whales' extract is only about 40 per cent of the standard, while the sperm whale extracts have only 8 per cent of the

TABLE 1

Antidiuretic effects of finback whale pituitary extracts

	POSTERIOR WHALE	INT. ST. PIT. POWDER	ANTERIOR WHALE	CONTROL
Gr. I	218	171	97	109
Gr. II	205	183	108	111
Gr. III	217	179	132	97
Gr. IV	210	191	104	99
Average	212.5	181	110.25	104

Figures represent time in minutes for maximum output after injection of pituitary extracts.

Each animal received 10 cc. of tap water at 37°C. intraperitoneally, and 0.5 cc. of dilute extract (0.25 cc. of extract (1 mgm. per cc.) diluted to 5 cc. saline).

activity of the standard beef solution. In other words, in the finback whale the proportion of pressor to oxytocic principle is more than 2:1, while in the sperm whale the proportion is 12:1.

THE FROG MELANOPHORE (CHROMATOPHOROTROPIC) HORMONE

There is general agreement that the melanophore hormone, the intermedin of Zondek and Krohn (10), is formed by the pars intermedia. It thus becomes a matter of special interest to determine whether this hormone is present in the pituitary glands of animals which lack a discrete pars intermedia, and if so, whether it is localized in the anterior or in the neural lobe. In the hypophysis of the chicken, in which there is also no pars intermedia as a separate zone, we found

the chromatophorotropic activity to reside in the anterior lobe, and not in the neural lobe. The same, we find, is true of both species of whales studied by us. Plate 2 illustrates this point very clearly. We may add that the melanophore principle can be extracted from the anterior lobe with dilute alkali, as well as with acid. Similar extracts of the desiccated neural lobe powder had no frog melanophore expanding action. Furthermore, treatment of the neural lobe acid extracts with alkali failed to develop this property. These tests prove that the melanophore hormone, when present, can be extracted with either acid or alkali, and that the hormone can not be regarded as a derived product formed by alkali treatment of the posterior lobe tissue itself or of the extracts made therefrom.

DISCUSSION

From Wislocki's observations on the porpoise and from Valsö's study of the blue whale, as well as our own work on the finback and sperm whales, it is clear that in the hypophysis of these mammals there is no pars intermedia recognizable as a discrete gross or histological entity. This structure is also absent in the chicken's pituitary gland in which, according to Bruni, the pars intermedia has failed to develop as a separate tissue, but has become incorporated with the anterior lobe. In these instances, where the usual site of formation of the melanophore principle, the pars intermedia, is missing, this hormone is found in the anterior lobe. On the other hand, in those mammals which do possess a distinct pars intermedia, this structure is so inseparably interdigitated with the neural lobe that the melanophore component is found in extracts made from posterior lobe (neural and intermediate parts). In the whale, as also in the chicken, extracts made from the neural lobe have no melanophore activity but do exhibit pressor, antidiuretic and oxytocic properties. It is thus evident that these latter principles are not elaborated by the pars intermedia, and hence the physiologically active components present in the ordinary posterior lobe extracts have a dual origin, the melanophore principle coming from the pars intermedia, the others from the neural lobe proper. These facts speak clearly against the view that the entire posterior lobe secretion is formed by the pars intermedia.

Another widely accepted hypothesis is that this secretion is derived

from the Herring bodies (11). These acellular structural elements, irregular in number, size, shape, staining capacity and distribution, are considered to be a secretion antecedent, migrating from cellular derivatives of the pars intermedia into the lumen of the third ventricle. In the whale and the chicken the Herring bodies are present in the neural lobe only and therefore cannot originate from the pars intermedia. Furthermore, we are permitted to say that there will shortly appear a paper in the *Anatomical Record* by Gersh (12), who reports experimental evidence indicating that the Herring bodies are artifacts and not precursors of the posterior lobe secretion. Additional evidence against the Herring bodies as being secretory antecedents which migrate into the lumen of the third ventricle and hence into the cerebrospinal fluid is furnished by the fact that recent and more refined assay methods have failed to reveal the presence of the pressor, antidiuretic and oxytocic components of the post-pituitary gland in the cerebrospinal fluid.

The simplest explanation in harmony with the facts is that the pressor, antidiuretic and oxytocic components are formed by the intrinsic elements of the neural lobe, even though none of its structures, with the exception perhaps of the pituicytes, are regarded as secreting elements in the ordinary sense. There appears to be no good reason for supposing that auto-pharmacological agents (Dale) can be formed only by cells of glandular tissues. It is conceivable that any metabolizing tissue may form compounds having specific physiological actions, and playing a definite rôle in the animal body when given off into the blood or lymph.

The prolonged submersion at great depths of the whale has been a matter of great scientific interest and many views have been put forward in explanation of this extraordinary fact. Our finding that in the whale hypophysis there is considerably more pressor than oxytocic material (in the sperm whale the ratio of the two principles is as high as 12:1) prompts us to suggest that this secretion may be one of the factors which enables the whale to remain submerged for long periods. The pressor principle of the posterior pituitary, when injected into animals, markedly reduces the oxygen consumption and slows the blood flow (13, 14). Hence it is conceivable that when the whale submerges, its hypophysis by pouring out its secretion, rich in the

pressor principle, so reduces the oxygen consumption and the blood flow of the whale that it can remain under water for a long time without coming to the surface for a fresh supply of air. Other factors, no doubt, are at work in this unique adaptive mechanism of the whale, and our suggestion, which, so far as we know, has not been advanced before, must be regarded as only a possible explanation of one of the contributory elements. A more complete discussion of this topic is given by Laurie (15) in his monograph dealing with the respiration of whales, and also by Irving (16).

SUMMARY

The pituitary gland of the finback (Balaenoptera physalus) and of the sperm (Physeter megalocephalus) whale is made up of a large flattened anterior lobe and a smaller posterior lobe separated by a septum. There is no discernible pars intermedia. Extracts of the acetone-desiccated posterior lobe powder of both species possess pressor, antidiuretic and oxytocic activity. The pressor and antidiuretic principle is present in the same concentrations as in the standard powder (beef), but the oxytocic principle is present in a much smaller concentration; in the finback whale there is about 40 per cent, while in the sperm whale only 8 per cent of the activity found in an equal weight of the standard powder. The melanophore principle is not in the posterior lobe, but in the anterior lobe. It is concluded that the pressor and oxytocic components are elaborated in the neural lobe, and are not derived from the pars intermedia.

The anterior lobe (see addenda to this paper) has the gonadotropic (follicle-ripening and luteinizing) hormones (the luteinizing principle in relatively smaller concentration, however, than in the sheep anterior lobe), and also the thyreotropic and adrenotropic principles (Lawrence). The prolactin content of the anterior lobe is very low; a good yield of follicle-stimulating hormone was obtained; and the presence of the thyreotropic factor was demonstrated (Riddle and Bates).

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ADDENDA

Several grams of desiccated anterior lobe powder of the finback whale were sent for assay purposes to Dr. Zonja Wallen-Lawrence of the Department of Physiological Chemistry and Pharmacology, University of Chicago, and a smaller quantity of sperm whale powder to Drs. Oscar Riddle and L. Bates of the Carnegie Station for Experimental Evolution, Cold Spring Harbor. We wish to express our appreciation to these investigators for their coöperation, and it is a pleasure to incorporate in this paper their reports, which follow.

AN ASSAY OF FINBACK WHALE ANTERIOR PITUITARY POWDER

ZONJA WALLEN-LAWRENCE

A gonadotropic preparation made from acetone-dehydrated and powdered anterior lobes of finback whales' hypophyses by a method described elsewhere[1] was injected once daily for four days into immature albino rats. Injections were begun on the day of weaning when the animals were twenty-one days old; necropsies were performed on the sixth day after the first injection. The dosage was variable as indicated in the tabulated data. The series of animals employed was necessarily small, being limited by the fact that only a small amount of material was available for assay, but by good fortune dose levels in the significant range were arrived at in the very first attempt.

In four of the injected animals, the vaginal introitus opened spontaneously on the fifth day after the first injection and the vaginal smear in each consisted almost completely of cornified epithelial cells, indicating that these animals were in oestrus. In one rat, the vaginal membrane ruptured on the sixth day after

[1] *J. Pharm. & Exp. Therap.*, 51 (1934), 264; figure 1.

the first injection and the smear contained nucleated epithelial cells and a few leucocytes. In the remaining three animals which received injections the vaginal introitus was closed at the time of necropsy. A correlation between vaginal response and the dosage is indicated in table I.

TABLE I

The effect of a gonadotropic extract made from whale anterior pituitary powder and injected subcutaneously once daily for four days into immature white rats twenty-one days old

Necropsies were performed on the sixth day after the first injection. Doses are expressed in equivalents of original whale pituitary powder. By *total dose* is meant four times the daily dose.

TOTAL DOSE	DAY OF VAGINAL RUPTURE*	VAGINAL SMEAR ON 5TH OR 6TH DAY	WEIGHT OF BOTH OVARIES†	WEIGHT OF UTERUS‡	WEIGHT OF THYROIDS	WEIGHT OF BOTH ADRENALS
mgm.		*cell type*	*mgm.*	*mgm.*	*mgm.*	*mgm.*
400	5	Cornified	27.0	48.0	8.6	18.0
400	5	Cornified	22.8	42.4	10.4	13.7
400	5	Cornified	18.1	39.6	10.0	18.2
200	5	Cornified	17.2	37.0	8.6	14.4
200	6	Nucleated	14.6	40.4	9.0	14.4
2000	Closed		14.2	29.0	10.0	11.7
100	Closed		17.5	20.6	12.4	15.5
100	Closed		15.4	25.9	11.7	15.2
000	Closed		14.8	20.5	12.4	15.5
000	Closed		16.2	18.2	8.5	12.6
740	6 partly open	Cornified	45.0§	92.0	17.8	17.6

* The day of opening of the vagina is counted from the day of the first injection.

† For fifty-five non-littermate controls killed previously to the above experiment, but from the same colony of rats, the mean ovarian weight and standard deviation was 14.76 ± 3.24 mgm.

‡ The mean uterine weight and standard deviation, for the same controls, was 20.60 ± 4.23.

These figures refer to animals killed at twenty-six days of age.

Pairs of ovaries weighing 23.7 mgm. or over and uteri weighing 32.2 mgm. or more have been considered significantly increased in weight.

§ This was the only ovary which showed signs of hyperemia and of luteinization.

Of the injected rats, only one (and that one of the three on the highest dosage) showed a significant increase in ovarian weight. Its ovaries weighed 27.0 mgm.:[2] the probability that by random sampling such an ovarian weight could be attained in an untreated animal is less than 0.01, hence the increase in weight is significant. The ovaries from the seven other injected animals cannot be con-

[2] Mean ovarian weight and standard deviation of control animals from the colony in question was 14.76 ± 3.24 mgm.

sidered significantly increased in weight. In the gross there was no evidence of hyperemia, luteinization or ovulation in any of the ovaries of the series.

The histological sections of the two pairs of ovaries weighing 27.0 and 22.8 mgm., respectively,[3] show the effect of a general stimulation to follicular development which involves nearly all follicles. No follicles in the experimental ovaries are as small as the smallest primordial follicles found in "nests" near the periphery of the ovaries of the littermate control. The follicles and ova from the experimental animals appear normal: the ova have not developed to the stage of maturation. The atresia which is observed is not any greater than the atresia which occurs in normal ovaries. The histological sections of the ovaries give no evidence of ovulation: the serial sections of the respective Fallopian tubes contain no tubal ova. There is no evidence whatsoever of luteinization.

The negative results with respect to luteinization *do not prove* that the luteinizing hormone is absent from the anterior lobe of the whale. The amount of luteinizing hormone injected may have been below the stimulating level for that hormone. So another attempt was made to bring about luteinization by injecting into one animal the total available whale material left. The total dose which was administered was equivalent to 740 mgm. of powder. The vagina of the rat receiving this dose did not open on the fifth day as did those on the 400 mgm. dose and it was only partly open on the sixth day after the first injection. This fact in itself, to one who has used perhaps 15,000 rats for gonadotropic assays and who is looking for luteinization, suggests that necropsy may reveal the beginnings of luteinization. At necropsy, the ovaries weighed 45.0 mgm.; the uterus, 92.0 mgm. In the gross the picture was preëminently that of follicular stimulation. However, two follicles in one ovary had begun luteinization. That luteinization was in progress was further suggested by the hyperemia of this ovary and the delayed vaginal canalization. Serial sections prove the presence of lutein tissue and show the characteristic increase in vascularity and strikingly dilated veins. There were no ova in the serially sectioned Fallopian tubes. It can be definitely concluded that luteinizing hormone is present in the anterior lobe of the whale pituitary body.

Turning next to the uteri. Five of the injected animals of the original series showed statistically significant increase in uterine weights. The mean weight of the five uteri was 41.48 ± 4.13 mgm. as compared with 20.60 ± 4.23 mgm. which was the mean weight and standard deviation of fifty-five uteri from normal untreated animals twenty-six days old and from the same colony. Histological examination shows mitosis in the lining epithelium, in the muscle and in the uterine glands. The lining epithelium is taller and contains more cytoplasm than in the untreated control. The differences both as to weight and histology show that uterine growth has been going on at an accelerated rate; the impetus to development must have been furnished by the injected whale-pituitary preparation.

The combined weights of the thyroids and parathyroids are also incorporated in the table: the weights probably have no significance. Similarly the histo-

[3] Ovaries and tube of the remaining six injected animals of this series were not histologically examined.

logical comparison between experimental and control thyroids and parathyroids shows no differences. But the rat thyroid is notoriously not a good indicator for anterior pituitary thyreotropic activity. For the purpose of determining whether the preparation contained thyreotropic properties a pair of guinea-pigs were used. One guinea-pig, weighing 134 gm., was injected once daily for two days: the total injection was equivalent to 200 mgm. of the original whale-pituitary powder. The other guinea-pig, weighing 148 gm., was kept as an untreated control. Both animals were killed on the fourth day after the first injection. The thyroids and parathyroids of the injected animal weighed 35.9 mgm.; of the control, 24.4 mgm. These values are perhaps significantly different; however, I cannot assert that such is the case because of not having examined a sufficient number of normal guinea-pig thyroids to be familiar with the normal variation due to random sampling. Professor Robert R. Bensley of the Department of Anatomy has examined the histological sections of the experimental and control thyroids and parathyroids. In the experimental guinea-pig thyroid, the epithelium is taller and the cells larger than in the control. The apparent vacuolation of the follicles around the periphery of the experimental organ is a phenomenon which Doctor Bensley has never before observed; usually the whole gland is so affected. The parathyroids show no deviation from normal. Doctor Bensley thinks the conclusion is warranted that the whale anterior pituitary extract did contain something which definitely affected the thyroid of the injected guinea-pig.

Lastly, the weights of the adrenals are incorporated in the table. To what extent the weights are significant I cannot state. Doctor Norman L. Hoerr, also of the Department of Anatomy, has examined the histological sections of the adrenals. He states that the cortex of the experimental animals shows hyperemia and is without question enlarged as compared with the adrenal cortex of the littermate control. Whether the increase in adrenal cortex be due to accumulation of lipoid or to oedema cannot be stated from the type of fixation which was employed. The probability is that the whale anterior-pituitary extract contained a factor which affects the adrenals of the rat.

Concerning the growth-promoting principle of the anterior lobe of the whale, no statement can be made because the material submitted for assay was too limited in amount to permit of such an investigation.

It has been convincingly shown that the powder submitted for assay contained a follicle-stimulating principle. This principle from the whale-pituitary, like the corresponding hormone from sheep, is strongly oestrogenic and can exhibit its oestrogenic power without necessarily causing significant weight increase in the ovaries. The presence of a luteinizing principle was likewise demonstrated. But this principle was not present in the same relative amount as in extracts similarly prepared from fresh sheep powder. The luteinizing potency was relatively low; whether it was low due to deterioration cannot be definitely stated. The whale-pituitary powder contained a factor affecting the thyroid gland of the guinea-pig: it contained a factor which affected the adrenals of the rat, chiefly the adrenal cortex. Whether the growth-promoting hormone is present or not was not determined.

AN ASSAY OF SPERM WHALE ANTERIOR PITUITARY POWDER

OSCAR RIDDLE AND L. BATES

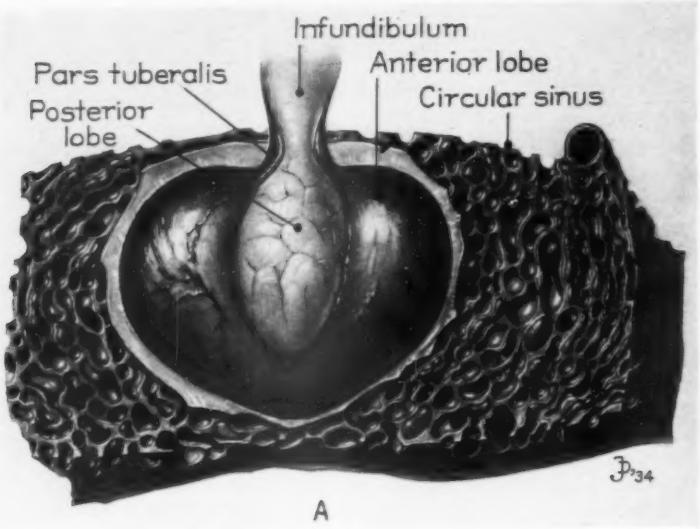
The 1.8 gm. sample sent was given three alkaline extractions which in our experience removes the anterior pituitary hormones. From our extract we recovered 120 mgm. of powder. We administered 40 mgm. of this powder to each of three birds (10 mgm. each per day for 4 days).

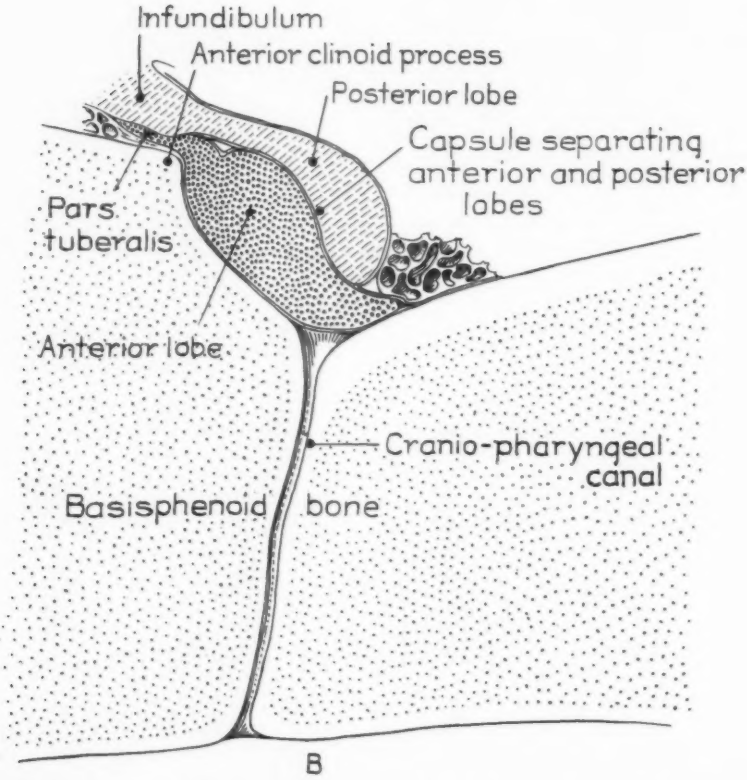
The material contains surprisingly little prolactin, only about 3–5 bird units in nearly 2 cc. dry tissue (probably 9 gms. (?) fresh tissue). From a similar quantity of beef pituitary anterior lobe we would obtain about 350 units. Beef pituitary is therefore approximately 100 times richer in prolactin than the sperm whale anterior pituitary. We have earlier found that both sheep and pig anterior pituitary give very poor prolactin yields (but better than the sperm whale).

A good yield of follicle-stimulating hormone was obtained. At present we are unable to express this in a suitable and well-defined unit. The 0.6 gm. dry powder (40 mgm. of our extract) during 96 hours produced an average increase of 1160 per cent in the testis size of the three immature male doves receiving it.

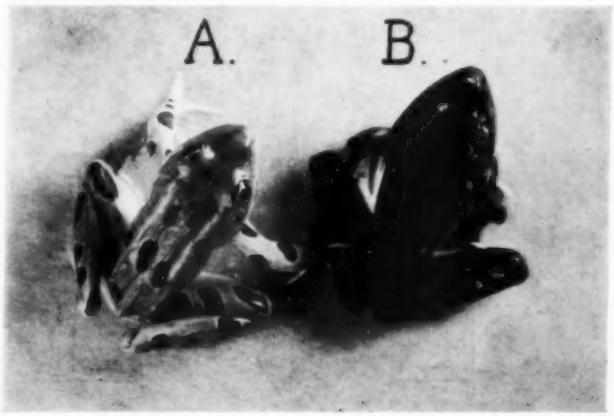
A demonstration of the presence of the thyreotropic hormone was secured by the thyroid weights of the three treated doves. Again we have no suitable way of expressing this in terms of units.

The short-term dosage had no consistent effect on the body weight of the three birds used—perhaps a tendency to produce loss of weight.





A Life Size Drawing of the Hypophysis of a Female Finback Whale



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Frog A injected with 0.3 cc. of posterior lobe extract (0.25% acetic of acid) finback whale (1 mgm. per cc.). No effect on melanophores.

Frog B injected with with 0.3 cc. of anterior lobe extract (0.05% acetic acid) of finback whale (1 mgm. per cc.). Marked expansion of melanophores.

THE BRAIN OF THE WHALEBONE WHALE, *BALAENOPTERA PHYSALUS*

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Through the kindness of Dr. E. M. K. Geiling it has been possible to examine the brain of an adult whalebone whale, *Balaenoptera physalus*, and the head of a fetus of the same species. The adult brain was suitable only for a study of surface form; the cranial nerves had been torn away in removal, owing to the fact that they run through a tough vascular sinus just outside the subarachnoid space. In the fetal head it was possible to follow the connections of the cranial nerves.

Marine mammals show remarkable adaptations to aquatic life; these have been described recently by Kellogg (1928) and by Howell (1930). These adaptations are mirrored in the form and structure of the brain. A comparison was made between this material and the nervous system of the porpoise, *Tursiops truncatus*, which I had studied previously (1932).

The adult brain fixed in formalin weighed 5.95 kilos. The transverse diameter across the widest portion of both cerebral hemispheres was 24 cm., and the longitudinal measurement of a cerebral hemisphere was 19 cm. The transverse diameter of the cerebellum was 18 cm. Probably the brain of the whale surpasses in absolute size that of any other animal.

The dorsal surface of the brain is shown in figure 1. An unusual mechanical change in the form of the brain has taken place with the shift of the nostrils to the dorsal surface of the head to form the blowhole, and the telescoping of the bones forming the cranial cavity. Thus the brain has become foreshortened in its antero-posterior axis and has an increased transverse diameter. This is seen clearly in the whale, but is even more evident in the porpoise. The convolutional pattern of the cerebral cortices is extremely complicated.

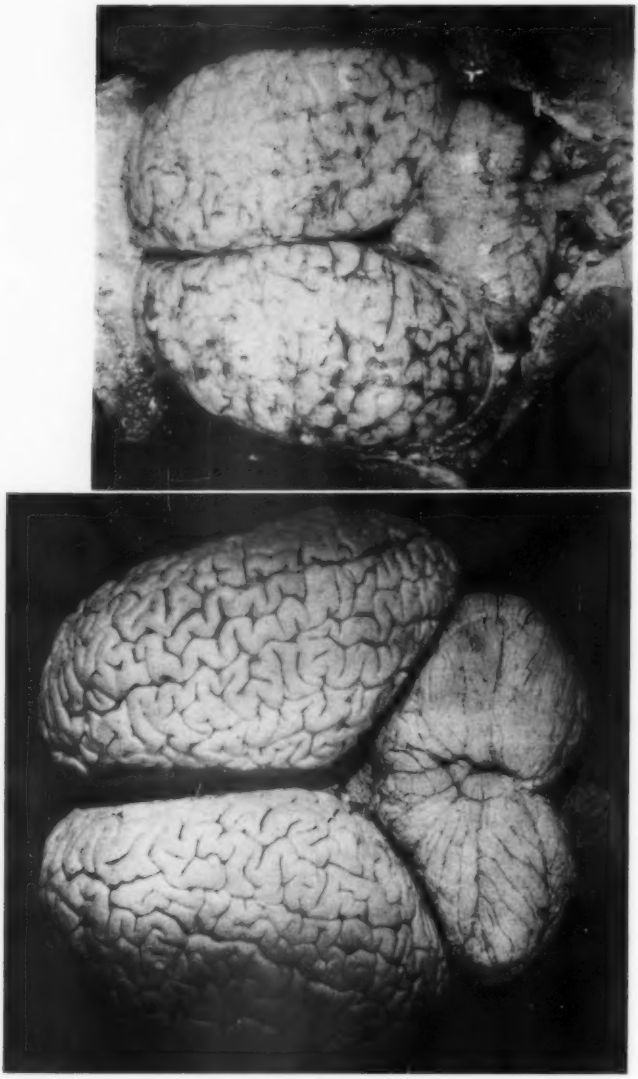

FIG. 1. THE DORSAL SURFACE OF THE BRAIN OF THE WHALEBONE WHALE, *Balaenoptera physalus*

The brain is foreshortened and increased in its transverse diameter as a result of adaptations in the cranial cavity. The convolutional pattern of the cerebral cortices is complicated; the cerebellum is large and has enormous connections with the cerebral cortex.

The shift in the axis of the cerebral hemispheres is evident on examination of the lateral surface. The fissure of Sylvius runs in a direction that is almost vertical. There is a large amount of cortex buried in this fissure and forming the island of Reil. On the lateral surface the gyri form a series of concentric rings around the fissure.

The frontal pole of the cerebral cortex is flattened and the frontal lobe extends far toward the ventral surface of the brain, in front of the fissure of Sylvius. In the porpoise the motor cortex lies on the frontal aspect, and it is probable that this is also true in the whale, although no histological preparations could be obtained. A provisional localization of the fissure of Rolando was made on this surface. This leaves but little cerebral cortex anterior to the motor area. The head of the caudate nucleus forms a promontory at the tip of the frontal pole.

The temporal lobe extends ventrally, behind the fissure of Sylvius. Near the temporal pole a considerable amount of olfactory cortex and the amygdaloid nucleus are exposed. These structures are separated from the neocortex by the rhinal fissure. It is probable that the occipital lobe forms the posterior pole of the cortex.

The hypophysis is connected to the infundibulum by a narrow stalk. The gland is flattened and lies in a very shallow sella turcica. The gland is almost entirely surrounded by a rich vascular plexus which encircles the stalk.

The cerebellum is large and can be divided into a vermis and two enormous hemispheres. The flocculus assumes considerable dimensions in water-living mammals; it is conspicuous here. As in the porpoise the pons is unusually well developed, and shows an abundant connection between the cerebral cortex and the hemispheres of the cerebellum, which probably insures precise control of muscular coordination.

The olfactory bulbs and tracts are present in the whale, although they are somewhat small. In the porpoise no olfactory bulbs or tracts are present, but one finds a moderate development of the so-called olfactory cortex. In the whale the olfactory cortex represents considerable differentiation. Olfactory structures as found in terrestial mammals are largely adapted to smelling through the medium of the air. Cetaceans apparently have found less and less need for olfactory structures. It is possible that in the porpoise the nerves have been

actually pinched off by the shifting of the cranial bones. It is difficult to imagine that for animals feeding under water the sense of smell is of much importance.

The optic nerve is not unusual in this brain. There is an optic chiasm, but it is not possible to estimate the number of fibers crossing at this point. In other cetaceans the decussation is said to be total. The eyes lie far to the side of the head, and there is no opportunity for binocular vision. The nerves to the extraocular muscles show nothing unusual. The trigeminal nerve is of great size; the second and third branches are well developed, whereas the ophthalmic branch is small. With the decrease in the importance of the olfactory sense, the trigeminal has apparently assumed greater importance in innervating the mucosa of the nasopharynx. The facial nerve is large so that it is capable of innervating the complicated musculature of the blowhole.

The ear has undergone unusual modifications in Cetacea since it has become adapted to respond to water-borne stimuli. The pinna has been lost and the external auditory meatus is completely closed in the whaleboned whales. The malleus is rigid and the tensor tympani muscle vestigial. The tympanic bulla is composed of dense bone. Water-borne stimuli transmitted to the air which it contains cause it to act as a sounding-box. Its vibrations reach the cochlea by way of the vesicular chain and vestibule.

In the porpoise the portions of the brain connected with the cochlear nerve were hypertrophied, so that one gained the impression that hearing was very important to the reactions of this form. The acoustic colliculi of the mid-brain were of greater size than the optic and the acoustic geniculates formed large prominences on the lateral surface of the thalamus.

In the head of the fetal whale it was possible to dissect the tympanic bulla, and study the relation of the malleus which fits into its lateral wall. The cochlea lies internal or dorsal to the tympanic bulla. The acoustic nerve and its connections are large in the whale but they do not reach the relative size found in the porpoise. The optic colliculi are larger than the acoustic in the whale. It would appear that hearing, while important in the whale, has not acquired the supremacy which it has in the porpoise. Perhaps the mere differentiation of this

special sense to function efficiently in a new medium has led to the increase in size of the cochlear nerve and its connections.

Little information could be obtained concerning the internal structure of the brain. The thalamus and corpus striatum are well developed. In transverse sections the remarkable infolding of the cortex and the large size of the centrum ovale are conspicuous. The pattern of the cerebral convolutions is more complicated than in the porpoise. The remarkable infolding of the cortical lamina is largely a result of conformation to the size of the cranial cavity, but may also be dependent on the vascular supply. Finally, it may be said that the brain of the whale shows the same trends of differentiation seen in the porpoise but the porpoise shows these specializations to a greater degree.

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VALUE OF THE INTRACUTANEOUS TUBERCULIN TEST IN THE DIAGNOSIS OF OCULAR TUBERCULOSIS

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Within recent years the quantitative intracutaneous tuberculin test (Mantoux test), has been widely used in the diagnosis of ocular tuberculosis. Opinions as to the value of the test, and as to the significance to be attached to its results are numerous and diverse. The present study represents an attempt to correlate the results of tuberculin tests with the preoperative clinical diagnosis and with the postoperative pathological diagnosis in cases of uveitis which have required enucleation of the affected eye. For the purpose of this investigation we have grouped together all cases of uveitis admitted to the Wilmer Institute since its opening in 1925 in which the affected eye was enucleated and in which a quantitative intracutaneous tuberculin test had been performed at a time when the intraocular inflammatory disease was clinically active. In all, fifty cases among 9000 admissions were found which conformed to these criteria. It will be seen that the cases were chosen irrespective of the results of the tuberculin test and irrespective of the clinical judgment of the nature of the inflammation. One patient was included on whom the tuberculin test had not been done, but who showed unquestionable evidence of old pulmonary tuberculosis, and on whom the test, if done, would almost certainly have been positive. We have counted this case among those giving positive skin tests.

TECHNIQUE OF THE MANTOUX TEST

The use of tuberculin in diagnosis and treatment at the Wilmer Institute is under the supervision of Dr. Leslie Gay who has described the technique elsewhere. The Koch's Old Tuberculin (O. T). which

is used for diagnosis has been prepared in the Henry Phipps Tuberculosis Laboratory of the Johns Hopkins Hospital. More recently the tuberculin has been prepared in the bacteriological laboratory of the Wilmer Institute. Each batch of tuberculin is carefully assayed by guinea-pig test.

PATHOLOGICAL EXAMINATION

In view of the difficulty of demonstrating tubercle bacilli in the ocular tissues we have based our pathological diagnosis on the finding of typical epithelioid-cell tubercles in the lesions. It is true that some instances of fungus infection and of syphilis give confusingly similar pictures, but fungi can be recognized readily by bacterial stain and no fungus infections were found in our series. Syphilitic lesions can usually be recognized as such, but no confusing cases were encountered in this series, that is, no case diagnosed histologically as tuberculous gave a positive Wassermann reaction or a history of syphilis. Sympathetic ophthalmia was found in two cases. Unless Mellor's theory is correct and all cases of sympathetic ophthalmia represent a special form of ocular tuberculosis these cases are not tuberculous, and were not so diagnosed in our series.

Routine sagittal sections were made through all the eyes examined. In all doubtful cases serial sections of the whole eye were studied. Ten of the fifty cases showed definite intraocular epithelioid-cell tubercles. Four of the fifty cases showed only the evidence of pre-existing inflammation without any cellular infiltration at the time of enucleation. These were cases of old uveitis complicated by glaucoma in which, owing to the congestion of the eye, a mistaken diagnosis of still active uveitis had been made clinically. In the old scarred lesions which we found in these cases we were unable to recognize any criteria which would tell whether the original lesion had been tuberculous or not. These cases we classified as undiagnosed.

Twenty-nine cases were clearly not tuberculous. In these there was definite evidence of some specific etiology other than tuberculosis, *e.g.*, pyogenic or syphilitic infection, intraocular foreign body, or sympathetic ophthalmia. In 7 no specific non-tuberculous cause for the uveitis could be established, but no tuberculous lesions were found even on serial sections of the whole eyeball. These were therefore

classified as non-tuberculous. In all of the cases diagnosed histologically as tuberculous the ocular lesion was active at the time of enucleation. The results of our analyses are shown in tables I to III.

DISCUSSION

The questions of primary interest toward which our investigation was directed were the following:

(1) Do patients with proven active ocular tuberculosis always give a positive Mantoux test?

(2) What diagnostic significance is to be given to the varying degrees of reactivity discovered with the Mantoux test?

(3) In the proper study of inflammatory intraocular disease, does a negative Mantoux test often lead to a false diagnosis?

TABLE I

Summary of pathological study

DIAGNOSIS	NUMBER OF CASES
Tuberculous	10
Non-tuberculous	36
Undiagnosed	4
Total	50

(4) In the proper study of inflammatory intraocular disease, does a positive Mantoux test often lead to a false diagnosis?

In answer to the first three questions the data summarized in table III are relevant. Of 10 cases of proven ocular tuberculosis 6 reacted to $\frac{1}{1000}$ mg., while only one failed to react to all dilutions below 1 mg. The proportion of strongly positive reactions in this group is much higher than in the general population. Extreme hypersensitivity to tuberculin is, therefore, of definite diagnostic significance in these cases. Moderate hypersensitivity to tuberculin producing reactions to $\frac{1}{10}$ or $\frac{1}{100}$ mg. is no more common in cases of proven ocular tuberculosis than in cases of non-tuberculous uveitis. No diagnostic significance can, therefore, be given to this degree of reactivity in relation to the ocular inflammatory condition. Finally, an essentially negative reaction to tuberculin can occur even in

TABLE II

Summary of cases studied

NUMBER	NAME	AGE	SEX	CLINICAL DIAGNOSIS	GENERAL SURVEY	TUBERCULOSIS SENSITIVITY	REASON FOR ENUCLEATION	RESULTS OF PATHOLOGICAL EXAMINATION
1	N. E.	43	M.	Chr. Uveitis LE	A & T. 1912 old fibrous tbc. in both apices	Not done	Pain; Glaucoma	Positive
2	B. A.	17	M.	Old Choroiditis; Phthisis LE		1/1000	Phthisis	Positive
3	C. R.	34	M.	Recurr. ret. hemorrhages; Scleritis & iritis O. U. Det. ret. RE		1/1000	Pain; Glaucoma	Positive
4	P. O.	27	F.	Uveitis RE; Phthisis LE	Infected tooth	1/1000	Phthisis	Positive
5	S. C.	3+	F.	Intraocular tumor?		1/1000	Ruptured globe	Positive
6	B. O.	18	M.	Chorioret. RE; Uveitis O. U. Sec. cat. LE	Urethral stricture; infect. tooth; sli. apical infiltration of lungs	1/1000	Pain	Positive
7	G. O.	41	M.	Acute glauc.; Pur. Conj. LE; Deep punctate keratitis RE	Chr. tonsil. & sinusitis; sli. fibroid infil. R. upper apex	1/1000	Pain; Glaucoma	Negative
8	J. A.	25	M.	Chr. Uveitis; Congenit. cataracts O. U.	Mediast. tbs. with 1 or 2 fibrotic spots R apex	1/1000	Pain	Negative
9	B. A.	40	F.	Perf. corneal ulcer RE		1/1000	Endophthal.	Negative
10	S. H.	38	M.	Choroiditis O. U.	Diabetes; Mellitus WR 4+	1/1000	Pain	Negative
11	B. A.	48	F.	Hem. Retinitis LE; Glaucoma O. U.		1/1000	Pain	Negative
12	C. A.	43	M.	Phthisis RE; Uveitis & sec. cat. LE	B.M.R. −13	1/100	Phthisis	Positive

TABLE II—*Concluded*

NUMBER	NAME	AGE	SEX	CLINICAL DIAGNOSIS	GENERAL SURVEY	TUBERCULOSIS SENSITIVITY	REASON FOR ENUCLEATION	RESULTS OF PATHOLOGICAL EXAMINATION
13	F E.	43	M.	Uveitis & sec. glaucoma RE	Tonsillitis; oral sepsis	1/100	Pain; Glaucoma	Positive
14	A. L.	12	F.	Chr. Uveitis; Sec. glaucoma LE	Pyorrhea; Chr. tonsillitis	1/100	Pain; Glaucoma	Negative
15	F. A.	57	F.	Sec. Glaucoma RE	Diabetes Mellitus; BP 212/105	1/100	Pain; Glaucoma	Negative
16	S. T.	40	M.	Exud. chorioretinitis RE		1/100	Suspected tumor	Negative
17	H. O.	59	F.	Chr. uveitis & kerato-iritis, bilateral		1/100	Pain; Glaucoma	Negative
18	M. I.	38	M.	Phthisis RE; Chr. uveitis OU	Sinusitis	1/100	Phthisis	Negative
19	S. A.	64	M.	Old uveitis; Sec. glaucoma RE		1/100	Pain; Glaucoma	Negative
20	B. O.	46	F.	Chr. iritis; Sec. glaucoma RE		1/100	Pain; Glaucoma	Negative
21	C. R.	25	F.	Chr. uveitis; Phthisis RE	Infected tooth; Chr. adenoiditis & pharyngitis	1/100	Phthisis	Negative
22	G. D.	14	F.	Uveitis O. U.; Phthisis LE	B.M.R. −20	1/100	Phthisis	Negative
23	L. E.	18	F.	Juvenile glaucoma O. U.	Chronic tonsillitis	1/100	Pain	Negative
24	F. R.	29	F.	Uveitis & phthisis LE	Valvular heart disease	1/100	Phthisis	Negative
25	L. I.	29	F.	Chr. uveitis O. U.; Phthisis L. E.	Wass. 4+; Infected teeth; Chr. sinusitis	1/10	Phthisis	Positive
26	P. A.	34	M.	Chr. uveitis; Sec. glaucoma O. U.	Wass. 4+; Hypertension; Infected tooth	1/10	Pain; Glaucoma	Negative
27	H. E.	35	M.	Phthisis bulbi L. E.	Chr. sinusitis; Chr. tonsillitis; Infected teeth	1/10	Phthisis	Negative
						1/10	Phthisis	Negative
28	H. O.	70	M.	Chronic uveitis; Sec. glaucoma LE		1/10	Pain; Glaucoma	Negative
29	G. O.	59	F.	Dissem. chor. RE; Cat. & sec. glaucoma LE	Obesity; hypertension	1/10	Pain; Glaucoma	Negative

30	M. A.	44	M.	Chr. uveitis; Sec. glaucoma O. U.	Infected tonsil tags; Infected teeth	1/10	Pain; Glaucoma	Negative
31	K. E.	73	M.	Uveitis; Sec. glaucoma RE	Oral sepsis; Sinusitis	1/10	Pain; Glaucoma	Negative
32	H. E.	55	M.	Chr. iridocyclitis RE		1/10	Pain	Negative
33	C. O.	51	F.	Old iritis; Sec. glaucoma RE		1/10	Pain; Glaucoma	Negative
34	B. U.	62	F.	Occluded pupil RE; Phthisis LE	Hypertension; Diabetes mell.	1/10	Phthisis	Negative
35	J. O.	45	M.	Chr. iridocyclitis RE	B.M.R. −14	1/10	Pain	Negative
36	M. I.	52	M.	Perf. corneal ulcer LE		1/10	Pain	Negative
37	B. A.	70	M.	Uveitis; O. U. Glauc. RE	Hypertension	1/10	Pain; Glaucoma	Negative
38	R. O.	62	M.	Uveitis; O. U. Glauc. RE	Chr. tonsillitis	1/10	Pain; Glaucoma	Negative
39	C. H.	77	M.	Phthisis LE; Iritis; Sec. glauc. RE	Oral sepsis; Arteriosclerosis	1/10	Phthisis	Undiagnosable
40	F. I.	28	M.	Old injury; Iritis; Sec. glauc. LE	Infected teeth; Hist. of antiluetic treatment Wass. (−)	1/10	Pain; Glaucoma	Undiagnosable
41	K. E.	76	F.	Iritis; Sec. glaucoma LE	Hypertension	1/10	Pain; Glaucoma	Undiagnosable
42	E. N.	26	F.	Chorio-ret; Chr. uveitis bilateral; Phthisis LE		1	Phthisis	Positive
43	R. O.	28	M.	Chr. iritis O. U.; Sec. glauc. RE	Wass. 4+; Chr. prostatitis; Post. urethritis	−1 mg.	Pain; Glaucoma	Negative
44	G. I.	26	F.	Sec. glauc. O. U.	Wass. 4+	1 mg.	Buphthalmos	Negative
45	N. E.	37	F.	Chorio-ret. RE; Phthisis LE	Visceroptosis	1 mg.	Phthisis	Negative
46	E. L.	49	F.	Uveitis; Sec. glaucoma LE	Infected tonsils	Neg.	Pain; Glaucoma	Negative
47	S. T.	5	M.	Chr. uveitis; Phthisis RE		Neg.	Phthisis	Negative
48	C H.	11	M.	Old uveitis; Staphy. cornea O. U.	Lupus erythematosus; infected antrum	Neg.	Staphyloma	Negative
49	S. K.	13	M.	Keratitis RE; Phthisis LE	Chronic tonsillitis	Neg.	Phthisis	Negative
50	W. A.	6 mo.	M.	Uveitis; Sec. glauc. RE		Neg.	Staphyloma	Undiagnosable

patients with active ocular tuberculosis. Such a negative reaction cannot, therefore, be taken as conclusive evidence that the ocular lesion is not tuberculous.

False negative reactions to the intracutaneous tuberculin test are, in fact, well known. In miliary tuberculosis the reaction sometimes becomes negative in the terminal stages when the body is overwhelmed with the infection. In less serious forms of tuberculosis the reaction at times becomes weak or disappears altogether in the course of febrile conditions no matter whether the fever is due to the tuberculosis or to some intercurrent disease. Some infections, such as influenza and measles, are known to have a specially marked effect in masking

TABLE III

Summary of cutaneous reactivity

TUBERCULIN SENSITIVITY	TOTAL NUMBER	PATHOLOGICAL FINDING		
		Tuberculosis	Not tuberculosis	Undiagnosed
mg.				
$\frac{1}{10000}$	11*	6	5	0
$\frac{1}{1000}$	13	2	11	0
$\frac{1}{100}$	17	1	13	3
1	4	1	3	0
Negative	5	0	4	1
Total.....	50	10	36	4

* Includes Case No. 1.

a tuberculin sensitivity. Loss of cutaneous reactivity often occurs in pregnancy. In the false negative case in our series none of these familiar circumstances were available to explain the negative reaction. Since the skin test led to an erroneous clinical diagnosis it seems desirable to report this case in detail.

Case 42. The patient was a white student nurse, aged 26, admitted to the Wilmer Institute on September 11, 1926. Until 1922 her eyes had been entirely normal. In that year she first noticed attacks of blurring of vision in the left eye which came and went, and were later associated with some redness of the eye but never with any pain. Within two weeks this eye became entirely blind except for light perception, and remained unchanged until her admission to the hospital. She occasionally had slight blurring vision in the right eye, but on the whole the vision of this eye has been quite good.

There was no history of tuberculosis in her family. Her general health had always been good, but since the onset of her eye trouble, she had been somewhat nervous and run down. During the previous winter she had had a severe cough lasting several months and several times had had blood-streaked sputum. In the afternoons she was usually markedly fatigued but did not have fever. Her weight had been 128 pounds in 1920; on admission her weight was 110.

On examination a large choroidal scar was found in the right fundus and a corresponding defect in the visual field, but there was no evidence of activity in the lesion. The left eye was somewhat small and shrunken; the iris scarred with numerous synechiae; the lens cataractous; vision was reduced to questionable light perception in the upper nasal field.

General physical examination revealed old middle ear deafness of the right ear; the lungs were clear both on physical examination and on x-ray; there was no evidence of sinus disease; two teeth showed periapical infection and were extracted. The blood and urine were normal; the Wassermann test was negative for the blood and spinal fluid; the tuberculin test was negative in all dilutions up to and including 1 mg.; the basal metabolism was −8 per cent.

The patient was discharged from the hospital on September 24, 1926 and re-admitted November 21, 1931. In 1927 she had had an attack of dimness of vision of the right eye with some redness and irritation, but this passed off without further trouble until October 1931, when the right eye again became inflamed and sensitive. For a few days she saw haloes about lights and her vision rapidly decreased. The examination in 1931 showed a very active inflammatory trouble in the right eye with peri-corneal congestion, heavy deposits on the posterior surface of the cornea, extensive deposits on the anterior capsule of the lens and beginning lenticular opacities. The left eye, while not congested, showed some fresh deposits on the posterior surface of the cornea in addition to the old scars. Vision was reduced to hand movements at 4 feet in the right eye, and to no light perception in the left, and the visual field of the right eye showed a concentric contraction. Neither fundus could be seen.

Physical examination showed again no evidence of pulmonary tuberculosis nor of foci of infection in her teeth, sinuses, gastro-intestinal or genito-urinary tracts. The laboratory tests gave results essentially the same as on the previous examination, except that there was a mild positive reaction to 1 mg. of tuberculin. In consideration of this and the previous skin test the case was regarded as non-tuberculous. It was thought possible that the blind left eye might be acting as a focus of infection in relation to the right eye and this was removed. Under local treatment the right eye improved somewhat and on discharge the patient could count fingers at one foot.

Following her discharge there were for a time no fresh symptoms, but her vision gradually became worse, and she returned on April 11, 1933 with a mature cataract in the right eye. There was no evidence of any active trouble at this time and a preliminary iridectomy was done without complications. On May 15, 1933, the cataract was removed, and on June 11, 1934, a capsulotomy was performed, the final vision being hand movements at 18 feet.

Pathological examination of the enucleated eye revealed a shrunken phthisical globe. The cornea and iris showed old scars but no active inflammatory infiltration. There was a calcareous cataract, an ossified cyclitic membrane, with funnel-shaped detachment of the retina. In the posterior portion of the choroid on one side, there was a large hyalinized tubercle 3 mm. in diameter, surrounded by a dense capsule of tuberculous granulation tissue. It is clear that at the time of enucleation the inflammation in the left eye was relatively inactive, but there is ample clinical evidence that it had been active in the right eye at the time when the skin test was positive to no less than one milligram.

To answer the fourth question as to how frequently a strongly positive tuberculin reaction leads to a false diagnosis of the nature of intraocular inflammatory disease we must turn to a more detailed analysis of the first eleven cases in table II. The first six of these were proved to be tuberculous. In five of them the clinical picture was strongly suggestive of a tuberculous lesion. The single exception, (Case 5) was in a child of 3 who had a large mass of tissue in the anterior chamber with a spontaneous rupture of the globe and an extension of the intraocular process under the conjunctiva. The clinical diagnosis of an intraocular tumor was made in this case and the finding of a large caseous tuberculous lesion came as a surprise to the clinician. Since strongly positive tuberculin reactions are particularly rare in very young children more significance should have been given to this clinical finding.

Of the five cases with extreme tuberculin hypersensitivity without ocular tuberculosis there were several in which there were no clinical grounds for believing the case to be tuberculous. Case 7 had acute glaucoma complicated by acute purulent conjunctivitis. There were some old organized cellular deposits on the posterior surface of the cornea of one eye. Ocular tuberculosis was not suspected clinically. Case 9 had a perforating corneal ulcer with panophthalmitis following what had presumably been a gonococcal conjunctivitis. Ocular tuberculosis was not suspected clinically. Case 11 had an obstruction of the central retinal vein in one eye with secondary hemorrhagic glaucoma. Numerous operations were performed for the relief of pain and tension and a subacute endophthalmitis eventually supervened requiring enucleation of the eye. Ocular tuberculosis was not suspected clinically.

Case 8 was in a young colored man with congenital cataracts who

developed bilateral severe uveitis following the extraction of his cataracts. He had mediastinal and pulmonary tuberculosis and reacted violently to tuberculin in the highest dilution, but the ocular inflammation was typically that of sympathetic ophthalmia. The case was falsely diagnosed as tuberculous, clinically.

In case 10 the patient had had a bilateral recurrent chorio-retinitis and had eventually become completely blind in one eye. In addition to being sensitive to tuberculin he suffered from diabetes and syphilis. The uveitis was thought to be syphilitic, but in view of its persistence in spite of antiluetic treatment the possibility that the ocular lesion might be tuberculous was considered by the clinicians. Histologically, the lesion was definitely syphilitic.

Of these eleven cases showing extreme hypersensitivity to tuberculin two were wrongly diagnosed clinically. In one the clinical picture was that of an intraocular tumor with perforation of the globe, and the evidence from the skin test was wrongly disregarded. The second was a case of sympathetic ophthalmia in a patient with mediastinal and pulmonary tuberculous lesions and was falsely diagnosed as ocular tuberculosis. It is apparent that even in cases of extreme hypersensitivity to tuberculin the results of the skin test can be taken as of diagnostic value only when considered in the light of all other clinical findings.

CONCLUSIONS

(1) Among patients suffering from proven ocular tuberculosis more than half show extreme hypersensitivity to tuberculin (positive reaction to $\frac{1}{1000}$ mg.).

(2) Moderate hypersensitivity to tuberculin (positive reaction to $\frac{1}{100}$ or $\frac{1}{10}$ mg.) is of no diagnostic value in relation to ocular tuberculosis.

(3) The absence of hypersensitivity to tuberculin (positive reaction to 1 mg. or completely negative reaction) does not completely rule out the possibility of ocular tuberculosis.

(4) In all cases the significance of the intracutaneous tuberculin test can only be evaluated when weighed in relation to all other clinical data.

RENAL RICKETS

Report of a Case Showing Four Enlarged Parathyroids and Evidence of Parathyroid Hypersecretion

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The association of late rickets and albuminuria was fully appreciated by Goodhart (1) in 1872 and by Lucas (2) in 1883, but it was not until 1911 that attention was called to the occurrence of bony deformities in renal disease. In that year, Fletcher (3) and Parsons (4) described typical cases of infantilism due to chronic renal disease, some of these presenting also rachitic lesions of the skeleton. In 1920, Barber (5) reported additional cases and defined "renal rickets" as a separate disease entity. Since then, many cases of renal rickets have been described, summaries of which have been made notably by Mitchell (6), György (7), and by Hamperl and Wallis (8).

Renal rickets is sometimes also called "renal infantilism" or "renal dwarfism." This is, indeed, unfortunate, since a multiplicity of names tends to confuse the conception of the essential nature of the disease. Strictly speaking, "renal rickets" should be applied only to those cases in which rickets results from chronic renal disease. Miller and Parsons' (9) cases of "renal infantilism" are, however, frequently quoted as examples of renal rickets, although the cases include not only rickets, but also infantilism "without renal disease (diabetes insipidus)." The patients falling under the latter grouping apparently showed neither rickets nor renal disease, the infantilism probably having been due to involvement of the *anterior* pituitary by the same disease process which affected the *posterior* portion and caused the symptoms of diabetes insipidus.

Renal rickets is also sometimes confused with *primary* hyperpara-

thyroidism, especially in young individuals. Before the establishment of the clinical syndrome of hyperparathyroidism, some such cases were included among cases of rickets; and since the demonstration of the assocation between osteitis fibrosa and hypersecretion of the parathyroids, cases of renal rickets or of chronic nephritis with parathyroid hyperplasia have been included in the realm of *primary* hyperparathyroidism. Thus, Davis-Coley's case (10), presenting malacia of the bones, tumor of the jaw, hypercalcinuria, and renal stones, which is probably rightly designated by Bulger, Dixon and Barr (11) as one of primary hyperparathyroidism, is mentioned by Mitchell (6) and others as an example of renal rickets. Hutinel's (12) case, which is also frequently cited as one of renal rickets, is probably another example of hyperparathyroidism or of a polyglandular disturbance, since the hypotonia, the pains in the knees, and the skeletal deformities antedated the albuminuria and the symptoms of impaired renal function by more than two years. Similarly, the occasional finding of parathyroid enlargement in nephritis is frequently confused with *primary* hyperparathyroidism, secondarily complicated by renal damage. Thus, in spite of the fact that the chronological data in MacCallum's (13) case of nephritis with parathyroid tumor, and in Hubbard and Wentworth's (14) case of extreme skeletal demineralization and metastatic calcification, clearly indicate that in both instances the nephritis was primarily responsible for the train of symptoms and for the pathologic findings in the tissues, Albright (15) cites them as instances of *primary* hyperparathyroidism with renal complications. In fact, the case recently described by Albright and associates (15) as hyperparathyroidism presented clinical and laboratory data which could have been explained as well, or better, by renal rickets—a possibility fully appreciated by them.

The confusion which exists between the two maladies is due to the fact that renal rickets may present all the cardinal clinical and laboratory findings of osteitis fibrosa of the osteoporotic type, complicated by impairment of renal function. In both, there may be polydipsia, polyuria, albuminuria, hyposthenuria, skeletal demineralization with deformities, azotemia, hyperphosphatemia, and a slightly decreased, normal, or even increased concentration of calcium in the serum—the latter, the usual finding in uncomplicated cases of hyperparathyroid-

ism, may occur in renal rickets, as in the cases described by Parsons (16), Duken (17), and Lightwood (18). The concentration of plasma or serum phosphatase may be increased in both diseases; the x-ray and histologic appearances of the bones may be impossible to differentiate with certainty; and the chief path of excretion of calcium in cases of osteitis fibrosa complicated by renal insufficiency may be the same as in renal rickets, *i.e.*, by way of the bowel. The parathyroid enlargement in osteitis fibrosa is usually confined to one or only two glands, as contrasted with the general hyperplasia which occurs in renal rickets; but this is not always the case, as, for example, the hyperplasia of only one gland in MacCallum's case of nephritis. The differentiation between the two disease entities therefore depends upon the history of events which led to the combination of skeletal demineralization and renal impairment, and upon the demonstration of an obstruction in the urinary tract—a finding frequently encountered in renal rickets. The courses in the two maladies may be traced as follows:

(a) *In hyperparathyroidism*, the changes in the skeleton antedate the renal symptoms. The patient may present, at first, all of some of the signs of hyperparathyroidism, such as hypotonia, lassitude, skeletal deformities, hypercalcemia, hypercalciuria, etc., but no symptoms suggestive of renal involvement except, possibly, polyuria. However, if the polyuria subsides, or the concentration of calcium in the urine increases, the excess calcium may precipitate in the kidney, the pelvis, or the ureters, and may ultimately cause impairment of kidney function. This impairment usually results in a modification in the calcium and inorganic phosphorus concentrations in the blood, and a shift of the excretion of calcium from the urine to the feces; in this respect, simulating the calcium and phosphorus metabolism in renal rickets.

(b) *In renal rickets*, the renal impairment precedes the skeletal changes. There is usually a history of the presence of symptoms of renal disease and of stunting of growth long before the skeletal deformities become evident.

When the insufficiency is due to a congenital defect in the genitourinary tract, as is usually the case in renal rickets, it is not always possible to obtain exact chronological data as to the impaired renal function. The case described by Albright and associates illustrates the difficulty which may sometimes be encountered in deciphering the

true course of events in any given instance, although it is possible that the enuresis and nycturia, which began in their patient two years prior to the skeletal symptoms, may have been the first signs of renal impairment. Definite proof for or against the existence of either renal rickets or hyperparathyroidism was not possible, since cystoscopy or retrograde pyelography was apparently not done and an autopsy was not obtained.[1] We have recently encountered a similar case in which the past history of the patient was of no avail as an aid in the diagnosis, and in which the clinical and laboratory data were not decisive of either primary hyperparathyroidism or of renal rickets, until shortly before exitus when ureteral obstruction and dilatation were demonstrated. The case is also of interest because of the finding of increased amounts

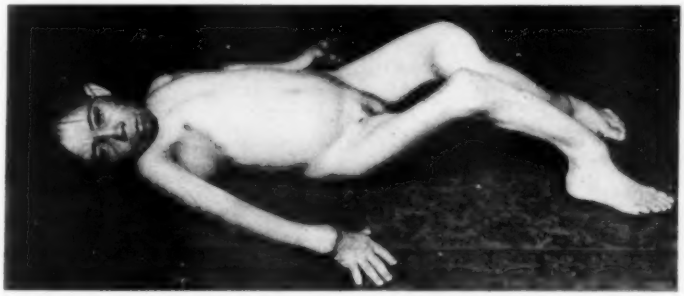


FIG. 1. PHYSICAL APPEARANCE OF PATIENT SHORTLY BEFORE EXITUS
Note the deformities of the chest and extremities

of parathyroid hormone in the blood, as determined by Hamilton's method (19), and of the discovery of four large parathyroids at autopsy. The latter finding has recently also been described by Smyth and Goldman (20), Langmead and Orr (21), and by Pappenheimer and Wilens (22).

CASE REPORT

L. S., a seventeen year old boy was admitted to the Harriet Lane Home of the Johns Hopkins Hospital, because of deformities and inability to walk. It was said that he was always small in stature, but well proportioned. He sat up,

[1] Personal communication.

walked, and talked at the usual time. His small stature did not arouse suspicion of any abnormal condition until about three years before his admission to the hospital, at which time he experienced pain in the left hip, lasting three weeks. Shortly afterwards, his left leg became progressively deformed; and a year later deformities also appeared in the right leg, arms, and chest. Three months before admission, he sustained a fracture of the right femur, as a result of being thrown against the front seat of a car when it suddenly came to a halt. Since then, he has been forced to remain in bed.

His relatives have no recollection of his ever having had acute nephritis or symptoms suggestive of renal disease. A definite history as to the exact onset of polyuria could not be obtained from the patient nor from his aunt, in whose care he has been since the separation of his parents more than five years ago. The only known acute illnesses of the past were whooping cough at one year, malaria at five, measles at six, and mumps at fourteen years of age.

TABLE I

Showing chemical findings in the blood

DATE	Ca	INORGANIC P	PHOSPHATASE UNITS	N.P.N.	Cl N/10	CHOLESTEROL	CO_2	PROTEIN	COMMENT
	mgm. %	*mgm. %*		*mgm. %*	*cc.*	*mgm. %*	*vol. %*	*gm. %*	
2- 7-34	9.6	8.0	22.1						
2-12-34	9.9	7.7		153	113				
2-28-34						208			
3-15-34				364	76		27	5.9 A/G 1.7	Vomiting
3-16-34 9 a.m.				302	81		46	4.7 A/G 1.7	Treated with NaCl and Na lactate
12 p.m.	9.3	10.5		287	82		48	5.1	

The physical examination revealed a markedly deformed and stunted boy of seventeen, whose height (117.5 cm.) approximated that of a boy of seven years (fig. 1) and whose weight was only 35 kilograms. The skin was pigmented, loose, wrinkled, and inelastic. The mucous membranes were pale, and the complexion was sallow. The heart was not enlarged. The arteries were hard and cord-like. The systolic blood pressure was 110 and the diastolic 72 mm. Hg. The kidneys could not be palpated with certainty, because of the extreme distortion of the chest, pelvis, and spinal column. The fundi, examined at the Wilmer Institute with the aid of a high-powered ophthalmoscope, revealed a slight degree of arterial narrowing in some areas and also a slight degree of arterio-venous compression.

The chemical findings in the blood, soon after admission, were as follows: calcium 9.6; inorganic phosphorus 8.0; cholesterol 208; and non-protein nitrogen 153 mgm. per cent. The concentration of chloride in the blood was 113 cc. N/10.

The basal metabolic rate was +3; and two sugar tolerance tests proved to be within normal limits. The serum phosphatase concentration was 22.1 units (Bodansky), the normal for his age being about 4 units. The subsequent chemical findings in the blood are tabulated in table I.

There was a moderate secondary anemia—58% (8.6 gm.) hgb. and 3.2 million erythrocytes per c.mm. of blood. The leukocytes numbered 10,000 per c.mm., 53 per cent being polymorphonuclear cells and 42 per cent lymphocytes. The morphology of the cells appeared normal.

The urine was of low concentration, the highest specific gravity being 1.010 and the lowest 1.006. It contained only a trace of albumin, but no sugar or formed elements. The excretion of phenolsulphonphthalein was less than 5 per cent in two hours.

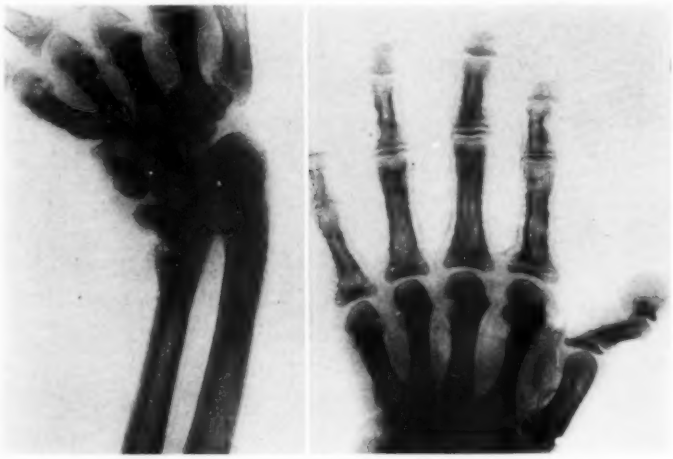


FIG. 2. X-RAY APPEARANCE OF HAND AND WRIST

Note the extreme rarefaction, the deformities, and the arterial calcification

A "balance" study of the metabolism of calcium and phosphorus as an aid in the differential diagnosis of renal rickets and primary hyperparathyroidism was not attempted, since in the presence of extreme impairment of renal function, the paths of excretion of these elements may be the same in both diseases, namely, by way of the intestines, as already stated.

The x-ray films showed calcification of the medium and small-sized arteries, including those of the fingers and subcutaneous tissues, and most profound demineralization and deformities of the entire skeleton, including the skull and vertebrae. The long bones, beside being extremely osteoporotic, appeared woolly and moth-eaten at their ends, and the metaphyses were moderately widened (figs. 2 and 3). The skull appeared mottled and woolly (fig. 4). The condition

of the calvarium could not be distinguished from that seen in advanced cases of Paget's disease or from that described by Dresser and Hampden (23) and Camp (24) as typical of von Recklinghausen's disease.

FIG. 3. X-RAY APPEARANCE OF THE FEET AND ANKLES, SHOWING DISTORTION OF THE BONES, MARKED DECALCIFICATION, AND ARTERIAL CALCIFICATION

Attempts to visualize radiologically the kidneys or areas of calcification in or about them were unsuccessful, largely because of the distortion of the chest, abdomen, and pelvis.

The laboratory findings just cited were not decisive in determining whether the case was one of renal rickets or of primary hyperparathyroidism, complicated

by impairment of renal function and by metastatic calcification. It then occurred to us that the presence or absence of hyperparathyroidism might be proved by using Hamilton's method for estimating increased amounts of parathyroid hormone in the blood. In this procedure, a rabbit is injected with the blood to be tested and is given known amounts of $CaCl_2$ by stomach tube, at stated intervals. Its serum calcium is then determined on blood drawn 15 minutes after the 0, 1, 3, and 5-hour administrations of $CaCl_2$. The calcemia curve is then compared with curves previously determined by using known amounts of parathyroid hormone instead of the patient's blood. Dr. Laslo Kajdi and one of us (D. H. S.)

FIG. 4. THE WOOLLY, MOTH-EATEN APPEARANCE OF THE SKULL AS SEEN IN THE X-RAY FILMS

have used this method to determine the concentration of parathyroid hormone in the blood of patients suffering from several skeletal diseases, including Paget's disease, xanthomatosis ossium, cases of renal rickets, and a case of osteitis fibrosa. The test was negative in all but three instances—the present case, a case of osteitis fibrosa, and a case of florid rickets of several years' duration. The result of this test, obtained with the patient's blood, is shown in fig. 5. Obviously, this test also failed as a means of differentiating the two maladies, since the concentration of parathyroid hormone in the patient's blood (1.5 units for 10 cc. of patient's blood injected, or 15 units per 100 cc.) approximated that which may be found in the blood of patients suffering from a moderate degree of primary hyperpara-

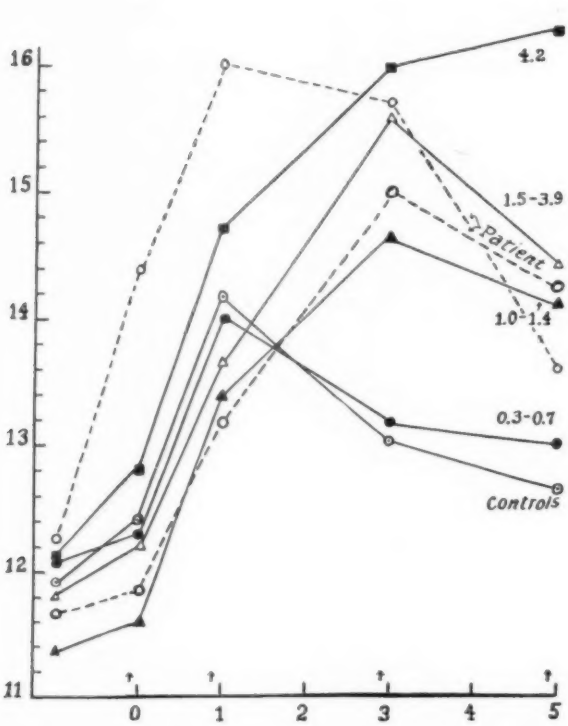


FIG. 5. "CALCEMIA CURVE" OF RABBITS INJECTED WITH THE BLOOD OF (1) A PATIENT WITH RENAL RICKETS (LOWER DOTTED LINE), AND (2) A PATIENT SUFFERING FROM OSTEITIS FIBROSA (HIGHER DOTTED LINE)

Compare with curves of rabbits injected with varying amounts of parathyroid hormone (Hamilton and Schwartz). Numerals at end of curves indicate units of parathyroid hormone injected; arrows denote $CaCl_2$ was administered (see text). Abscissa, Ca in mg. per cent; ordinate, time in hours. The first figures are the initial serum calcium values. before the administration of $CaCl_2$. The approximate concentrations of parathyroid hormone in the 100 cc. of the patient's blood may be calculated by comparing the "calcemia curves" with that obtained with known amounts of parathyroid hormone and multiplying by 10, since only 10 cc. of blood had been used. Thus, the blood of the first patient contained about 15 units; and that of the second patient contained more than 42 units of parathyroid hormone.

thyroidism. The negative tests in other cases of renal rickets will be discussed presently.

Since renal rickets is frequently associated with congenital anomalies of the genito-urinary tract, an attempt was made to determine, by pyelography, the size and shape of the kidneys and also the presence or absence of dilatation or distortion of the pelvis, ureter, or bladder. Intravenous pyelography was unsuccessful, probably because of the failure of the kidneys to excrete the opaque substance. Cystoscopy and retrograde pyelography were therefore attempted on March 10, 1934, but the pyelography had to be discontinued before its completion, as it was impossible to insert the catheter past an impassable obstruction in the left ureter. There was no immediate reaction following this procedure; but two days later, the patient complained of severe pain in the left lower abdomen and in the region of the left kidney. The pain was unbearable and could be relieved only by large doses of morphine (5 mg. every four hours). He became drowsy, refused all food, and vomited whatever food and fluid he had been forced to take. The urine became grossly bloody and later contained innumerable white cells. His general condition became worse. He appeared dehydrated and acidotic. The concentration of chloride in the blood decreased to 76 cc. N/10, the CO_2 to 27 volumes per cent, and the non-protein nitrogen increased to 364 mg. per cent. Six hundred cc. 1/6 M racemic sodium lactate was given intravenously and 600 cc. subcutaneously. This was followed by 1,800 cc. of 0.9 per cent solution of NaCl intravenously. These amounts were calculated to increase the carbon dioxide concentration 20 to 25 vol. per cent and the chloride to about the previous level. Four hours afterwards, the carbon dioxide in the blood increased to approximately the calculated value, namely, 48 volumes per cent, but the concentration of chloride increased only slightly—from 76 to 82 cc. N/10. A portion of the injected sodium chloride apparently found its way into the urine, as nearly 2300 cc. of urine was collected during that day. The condition improved somewhat after the infusion, but soon stupor developed and death occurred on the following day.

A blood culture, taken shortly before exitus, revealed the presence of hemolytic streptococcus albus.

An *autopsy* was performed nine hours after death. The following is a summary of the important findings:

The body is greatly deformed. The deformities involve both arms and legs, as well as the chest, pelvis, and spine.

The myocardium appears normal, except that it is perhaps slightly brownish. The valves are also normal in structure, and the coronary arteries are situated in their usual positions and are patent throughout.

The lungs appear to be air-containing throughout, except for a few scattered nodules which, on section, appear to be small abscesses, although there are no hemorrhagic areas about them.

The abdominal organs are situated normally. With the exception of those forming the genito-urinary tract, they appear normal on gross inspection.

The spleen weighs 45 gm. and measures 8 x 4 x 3 cm. On section, a grating sensation is felt. This is apparently produced by the sharp calcified arteries which are visible on the cut-surface of the organ. The spleen itself is of a peculiarly firm consistence.

The liver appears normal on gross inspection, except for a few small abscess-like areas.

The pancreas, stomach, and intestines show nothing unusual. The mesenteric artery seems somewhat thickened, but grossly no definite calcification is made out.

The kidneys show extreme changes. Each weighs between 60 and 70 gm. and measures approximately 9 x 5 x 3 cm. The capsule strips with moderate difficulty, revealing a completely irregular surface, marked by diffuse scarring and studded with wide-spread conglomerate abscesses. There is a slight grating on section of these organs, and in the pelvic regions calcified vessels can actually be palpated. The renal artery itself seems not to be involved.

The cut surface shows extraordinary distortion. There is extreme dilation of the pelvis and thinning of the tissue between it and the cortical margin—the result of long-standing hydronephrosis. The remaining renal substance varies from that in which the pattern is distorted by scar tissue to that in which it is swollen by the apparent acute inflammation and by the presence of numerous fresh abscesses. The renal substance measures only a few mm. in some areas and more than 1 cm. in others.

The pelvis of each kidney is markedly dilated and the walls are thickened. Both ureters are enormously dilated, measuring about 3.5 cm. in circumference. When opened, they show valve-like structures throughout their course. The linings are rough and the walls thickened. Each ureter is traceable to its opening into the bladder, at which points obstruction could not be demonstrated.

The bladder wall is somewhat thickened, and the mucosa on the posterior wall is thrown into very prominent folds, the surfaces of which are blood-stained. The urethra shows no obstruction or valve-like structures which could explain the cause of the dilatation throughout the urinary tract.

The prostate, testes, and seminal vesicles are somewhat smaller than usual.

The neck organs appear normal, except for the parathyroids. These are identified as greatly enlarged masses, symmetrically located at their usual sites (fig. 6-B). They appear to be hypertrophied, since they retain the usual shape of normal-sized glands. The upper glandules measure 1.9 x 0.8 x 0.3 cm. and 1.7 x 0.7 x 0.3 cm., respectively; and the lower ones measure 1.5 x 1.0 x 1.0 and 1.3 x 1.0 x 0.6 cm. They are of a grayish brown color.

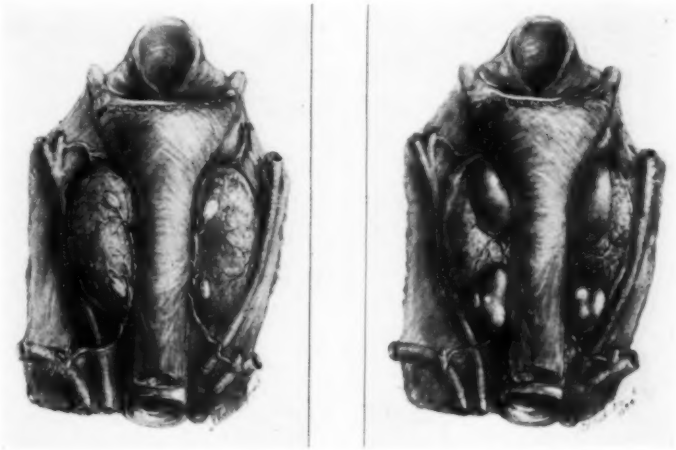
Sections through the costochondral junctions of the ribs show most extreme deformities. The line of ossification has lost all semblance of regularity and is composed of islands of cartilage. Much of the marrow in this vicinity is replaced by gray tissue, probably fibrous tissue. The same features are seen in the upper end of the femur. A section from one of the vertebrae shows mottled gray areas diffusely scattered through the centrum. The intervertebral discs appear normal.

The skull is enormously thickened (1 cm.), it appears mottled and soft, and cuts with the greatest of ease.

The aorta is fairly elastic and shows no gross changes. Calcification is seen throughout the course of the splenic artery but is only suggestive in the mesenteric artery. Grossly, the splenic artery and the branches of the renal arteries are the only ones showing calcification.

The brain and the meninges appear normal on gross inspection. The blood vessels at the base of the brain show no gross changes.

The hypophysis is fairly large, but it is symmetrical and normal in gross appearance.



A B

FIG. 6. THE APPEARANCE OF THE FOUR ENLARGED PARATHYROIDS IN OUR PATIENT (B) AS COMPARED WITH THE SIZE OF NORMAL PARATHYROIDS (A)

Histologic examination of the various organs and tissues reveals the following:

Thymus—General atrophy and calcification in a few of Hassall's bodies.

Lungs—A few small abscesses are seen. Their centers are filled with polymorphonuclear cells.

Kidneys—Sections of the kidney show most extensive acute inflammatory changes which make it somewhat difficult to interpret the primary or preëxistent changes. There are, however, some areas which are free from the acute necrotizing process and show marked scarring and infiltration with round cells. The amount of tissue between the cortical margin and the pelvis is markedly reduced and is composed of scar tissue, hyalinized glomeruli, and a few dilated tubules which are filled with pinkish-blue staining material. Some areas show one or two enlarged glomeruli and dilated tubules, the lumina of which are either free of

formed elements or contain hyaline casts. The entire picture is that of an acute inflammation superimposed upon an old pathologic process, the latter resembling the histopathology of chronic pyelonephritis.

Renal Pelvis—Sections from the dilated renal pelvis show great thickening and scarring of the wall, with some edema and scattered cell-infiltration. The mucosa has been apparently lost in the inflammatory process. The *ureters* show similar changes.

Blood Vessels—No lesions are seen in the aorta. Marked calcification is present in the splenic artery and in its ramifications in the spleen and the pancreas. The lumen of the artery is greatly reduced (fig. 7). Calcification of a lesser degree is also present in the mesenteric artery and its branches. In the larger vessels, the calcification is in the medial coat, and in the smaller branches it tends to be deposited along the line of the inner elastic lamella. Dark purple-staining material,

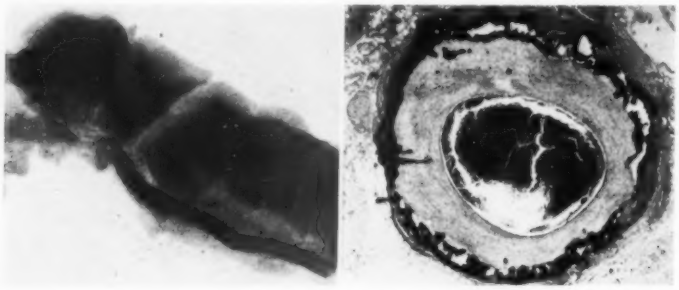


FIG. 7. ROENTGENOLOGICAL AND HISTOLOGICAL APPEARANCES OF THE SPLENIC ARTERY, SHOWING MARKED CALCIFICATION

probably the site of calcium deposition, is also noted along the line of the inner elastic lamella in the renal artery.

Thyroid—Acini are normal in size and contain normal amounts of colloid.

Parathyroids—Sections from all four enlarged glandules show no abnormal tissue, except that the normal-looking cells are packed closely. At least three types of cells may be seen: (1) cells with pale-staining cytoplasm; (2) cells of a similar character but which have a predilection for eosin; and (3) cells resembling the other types, except that their arrangement suggests a glandular structure (fig. 8). The histopathology of these glandules is that of hyperplasia, since the increase is in the number of cells rather than in their size or morphology.

Brain and Spinal Cord—No lesions noted.

Hypophysis—The anterior lobe shows several fairly large areas of necrosis, without cellular reactions about them. The rest of the hypophysis appears normal.

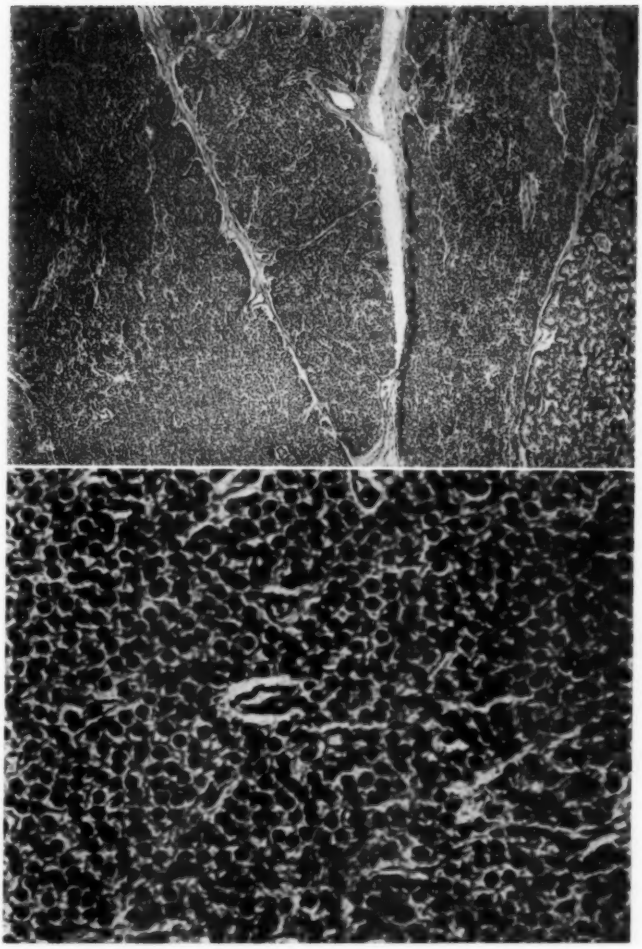


FIG. 8. HISTOLOGICAL APPEARANCE OF THE HYPERPLASTIC PARATHYROID

Note that the cells are normal-looking, except that they are packed closely, thus denoting hyperplasia.

Adrenals—No lesions seen.

Bones—Sections of rib show great distortion of the normal architecture (fig. 9). The line of ossification at the costochondral junction is extremely irregular and twisted, and the junctional cartilage cells are devoid of the usual columnar arrangement. The proliferative cartilage cells, which are so numerous in infantile rickets, are but few, and there is absolutely no evidence of ossification in them, although in the distal cartilaginous zone there is some indication of a previous attempt at

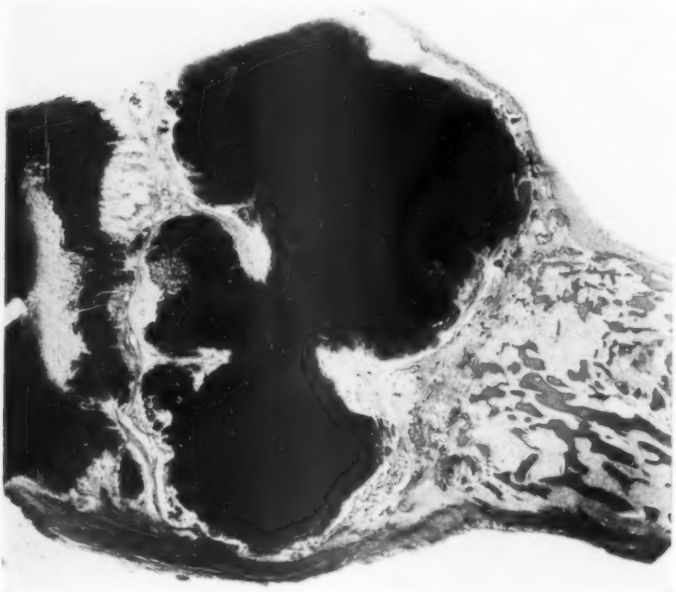


FIG. 9. MICROPHOTOGRAPH OF RIB, SHOWING ENLARGEMENT AND DEFORMITY OF THE COSTOCHONDRAL JUNCTION, OVERGROWTH AND IRREGULARITY OF CARTILAGE ZONE, SLIGHT CALCIFICATION IN THE METAPHYSIS, MARKED FIBROSIS, AND A PAUCITY OF OSTEOID TISSUE

calcification. Immediately adjacent to the cartilage cells, the tissue is composed of a few remnants of trabeculae and a most extensive fibrosis. The fibrosis extends from the cartilaginous zone into the marrow spaces of the shaft. The fibrous tissue contains numerous giant cells, blood vessels, poorly calcified spicules of bone without osteoid borders, and also many cyst-like areas of microscopic size (fig. 10).

Skull—The thickness of the skull is about 1 cm. There is a disappearance of division between the inner and outer tables and the intervening trabeculae, or diploe. The marrow spaces between the trabeculae seem to be entirely replaced by fibrous tissue and many dilated blood vessels. The fibrous tissue contains osteoclasts and multinucleated cells, but no definite cysts (fig. 11). The trabeculae are poorly calcified and are devoid of osteoid tissue.

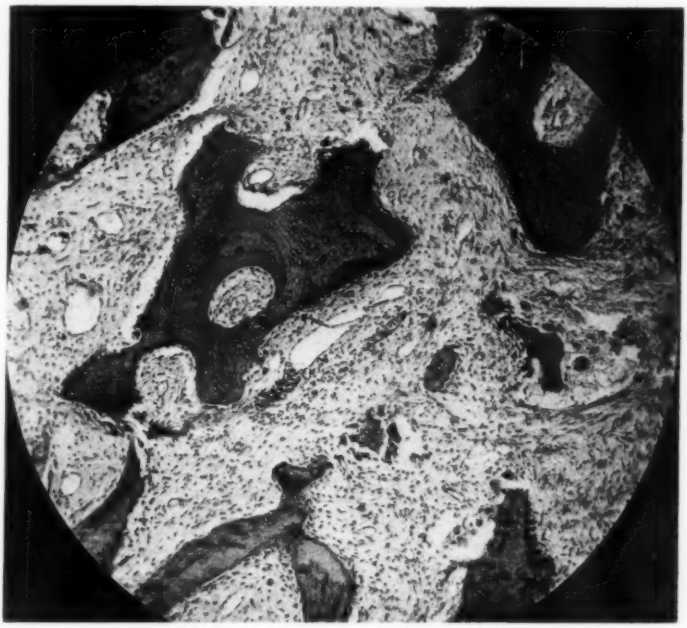


FIG. 10. HIGHER MAGNIFICATION OF FIG. 9, SHOWING FIBROSIS, SPICULES OF BONE WITHOUT OSTEOID BORDERS, GIANT CELLS, AND MICROSCOPIC CYST-LIKE AREAS

Vertebrae—The histologic changes in the vertebrae are nearly identical with those of the skull, and are indistinguishable from those of the osteitis fibrosa of von Recklinghausen, due to primary hyperparathyroidism.

Bone-Marrow—Section of femur marrow shows numerous areas in which there is hyperplasia of the blood-forming elements, and also areas in which there is fibrous tissue.

The autopsy therefore revealed: (1) great hypertrophy, dilation, and trabeculation of the lumina of the ureters; (2) extreme reduction of kidney substance

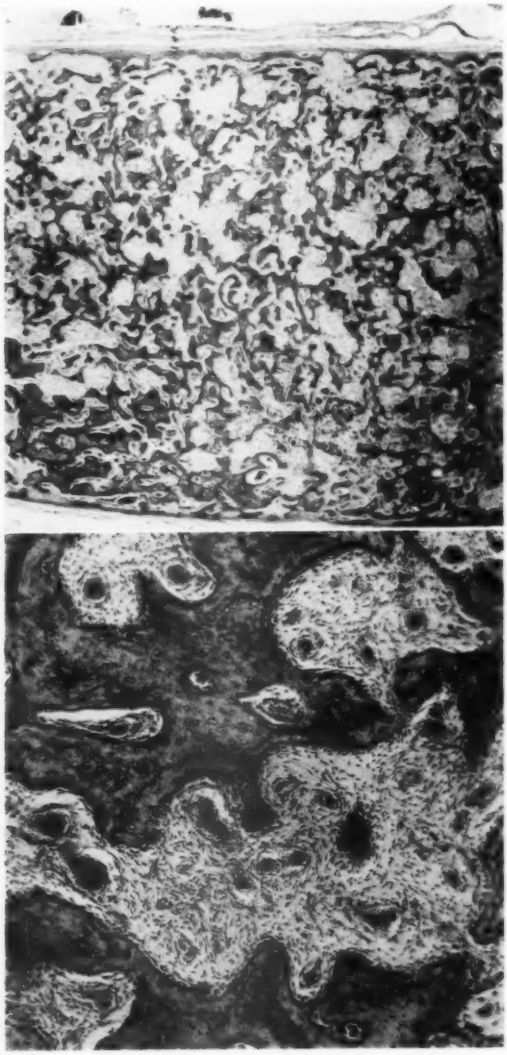


FIG. 11. MICROPHOTOGRAPH OF SKULL, SHOWING OSTEOID-FREE TRABECULAE, GIANT CELLS, AND REPLACEMENT OF MARROW BY FIBROUS TISSUE

and dilation of each pelvis; (3) acute and chronic cystitis, ureteritis, pyelonephritis, and pyonephrosis; (4) hyperplasia of all four parathyroids; (5) metastatic calcification of systemic arteries; (6) softening and deformities of the skeletal system, the histopathology of which resembles that of osteitis fibrosa; and (7) evidence of a recent bacteremia with metastatic abscesses.

COMMENT

The difficulties in differentiating between renal rickets and primary hyperparathyroidism on clinical, chemical, and roentgenologic grounds have already been mentioned; and the histologic studies further corroborate the fact that the bones from patients with renal rickets may simulate, in nearly every respect, those of individuals suffering from the osteoporotic type of osteitis fibrosa. The histopathology of the bones in our case resembles, in many respects, that exhibited in the cases of renal rickets described by Paterson (25), Greene (26), Hamperl and Wallis (27), and Shipley and his coworkers (28), but its resemblance to the condition seen in authentic cases of von Recklinghausen's disease is even more striking. Indeed, without the knowledge of what was found in the genito-urinary system, it would be impossible to differentiate the two diseases solely by histologic examination of the bones. On the other hand, these changes in the bones are not to be considered as pathognomonic of von Recklinghausen's disease, since, according to Jaffe (29), similar lesions in the bones may be brought about by a variety of agents, such as low-calcium diets and mineral acids. Accordingly, the changes in the bones of our patient may be interpreted as indicative of either a metabolic derangement associated with impaired renal function or of a primary or secondary hypersecretion of parathyroid hormone.

The association of renal impairment and hypertrophy or hyperplasia of the parathyroids has been noted by MacCallum (13) as early as 1905. At that time, MacCallum wondered about the relation of parathyroid enlargement and chronic nephritis, and he therefore examined the parathyroids in two other patients with nephritis, but found them to be normal. Subsequently, cases of nephritis in which the parathyroids were enlarged were also reported by other observers, but from many of these reports it is now impossible to tell whether the nephritis was primary and the parathyroid hypertrophy secondary, or whether the parathyroid hyperplasia was primary and the renal im-

pairment secondary. In some of these cases, the chronological data indicate that nephritis antedated the skeletal changes; in others, that the bone deformities preceded the impairment of renal function; and in still others, that the course of events in the development of the disease can only be surmised from certain clinical and anatomical findings. Thus, it is quite probable that the cases presenting hypertension, cardiac hypertrophy, contracted and scarred kidneys, and but little demineralization of the skeleton, were instances of chronic nephritis in which the parathyroids were secondarily involved; whereas the cases showing marked skeletal decalcification, nephrocalcinosis or nephrolithiasis, without hypertension or cardiac hypertrophy, were examples of primary hyperparathyroidism with renal complications. In the case of renal rickets, hypertension and cardiac hypertrophy may be absent, in which case the renal impairment is usually due to the presence of a hydronephrosis, the result of a congenital or acquired obstruction in the genito-urinary tract. In any event, in cases where there are definite histories or anatomic findings of nephritis or of congenital anomalies of the genito-urinary tract, the parathyroid enlargement may justly be looked upon as a secondary hyperplasia.

What initiates this hyperplasia is not definitely known. However, certain experimental observations on the metabolism of calcium and phosphorus in hypo- and hyperparathyroidism strongly suggest that the retained phosphate may be the impetus for the parathyroid hyperplasia (15, 20) and for the secretion of excess parathyroid hormone, as was demonstrated in our case. It is now a well established fact that hypoparathyroidism is associated with an inability on the part of the kidneys to excrete appreciable amounts of phosphate and that the phosphate, so retained, can be excreted in the bowel as the insoluble salt of calcium or of other cations capable of forming insoluble phosphates (30). There is also sufficient clinical and experimental evidence to show that parathyroid hormone is capable of initiating a phosphate diuresis in patients with tetany and thereby alleviating their symptoms (31, 32), and also of increasing the urinary phosphate excretion in the absence of tetany (33, 34). Apparently, the parathyroids are concerned not only with the metabolism of calcium but also with that of phosphate; and since it appears from the above data that one of the chief functions of the parathyroids in the body is to regulate

the excretion of phosphate, especially by way of the kidneys, it is reasonable to assume that the greater the phosphate retention the greater the burden on these glands to secrete parathyroid hormone in an attempt to rid the body of the excess phosphate, *i.e.*, their hypersecretion is compensatory.[2] Indeed, parathyroid enlargement in experimental rickets has been noted more often in instances where the diet was low in calcium and relatively high in phosphorus than when the metabolic disturbance was in the opposite direction, namely, high in calcium and low in phosphorus (35). Even the histology of the bones in experimental low calcium rickets and in renal rickets has many points of resemblance to that in the osteoporotic type of von Recklinghausen's disease (29), thus indicating that some common factor or factors are responsible for the demineralization. In renal rickets, therefore, the decalcification may be due to the phosphate retention and to the excretion of phosphate in the bowel as the insoluble salt of calcium (6), and also to the enlarged parathyroids, which are probably secondarily involved, but which may, nevertheless, augment the resorption of lacunar and spongy bone by secreting an excess of hormone. It is also possible that the chronic acidosis (36) and the retention of electrolytes and non-electrolytes play some part in the process of decalcification.

As previously mentioned, parathyroid hyperplasia, increased amounts of parathyroid hormone in the blood, and skeletal decalcification are not constant findings in chronic nephritis or in renal rickets. They are probably the exception rather than the rule. The presence or absence of these findings may be due to differences in the clinical course of the disease, the degree and duration of phosphorus retention, and the availability of calcium in the diet to correct this retention.

Although metastatic calcification in the soft tissues is quite common in both primary hyperparathyroidism and in renal rickets, nevertheless, there are some points of difference. In the former disease, the abnormal deposition of calcium salts usually begins in the kidneys, in

[2] Parathyroid enlargement in rats has recently been produced by reducing the kidney substance by unilateral nephrectomy, followed by destruction of part of the opposite kidney by thermo-cautery. (Jarrett, W. A., Peters, H. L., and Pappenheimer, A. M., *Proc. Soc. Exper. Biol. & Med.*, **32**, 1211, 1935).

the form of nephrocalcinosis or nephrolithiasis, due largely to the excretion of large amounts of lime salts by way of these organs; whereas, in renal rickets, because of the failure on the part of the kidneys to excrete lime salts, the metastatic calcification usually occurs in sites other than the kidneys, so that nephrolithiasis or nephrocalcinosis are rare findings in this disease. In our patient, nephrolithiasis and marked nephrocalcinosis were absent, the calcinosis being present mostly in the blood vessels.

More recent analyses of the reported cases of renal rickets seem to indicate that in children and adolescents the disease is usually due to a chronic obstruction in the lower urinary tract. Thus, of the twenty cases reported by Ellis and Evans (37), seventeen of which were studied anatomically, fourteen showed dilatation of the ureters, indicating obstruction in the lower genito-urinary tract. The cases reported by others, as well as our case and the one recently described by Smyth and Goldman, presented similar lesions. The involvement of the bladder in nearly all cases suggests that the urinary obstruction must be below the bladder, but, unfortunately, it is not always possible to demonstrate such an obstruction nor to find abnormalities in the nervous system which might account for a "functional" obstruction. Ellis and Evans suggest that "the underlying lesion is a functional failure of the vesico-urethral sphincter, either the occurrence of spasm, or as is more probable from what is found elsewhere, a failure of relaxation." They believe that the origin of this condition is congenital.

Very little can be accomplished therapeutically in advanced cases of renal rickets. Diets high in calcium and low in phosphorus have been suggested (38), but such therapy is merely palliative. Vitamin D is, of course, contraindicated; and we see no reason for attempting to extirpate one or more enlarged parathyroids.

The cause of the dwarfism in renal rickets is not definitely known. It is possible that it is due to the general disturbance in mineral and protein metabolism resulting from the renal insufficiency, or it may be due to some substance elaborated by the hyperfunctioning parathyroids. The latter hypothesis is suggested by the experiments of Thompson (39). Thompson showed that, aside from the calcium-raising principle, which he destroyed by heating parathyroid hormone with alkali, the extract contains a growth-inhibiting substance. The

finding of necrosis of the anterior lobe of the pituitary in our patient would seem to suggest that retardation of growth may have been due to hyposecretion of the growth-promoting principle of this gland, but definite proof for this suggestion is wanting.

SUMMARY

1. A case of renal rickets is reported in which increased amounts of parathyroid hormone in the blood were demonstrated *ante mortem* and four enlarged parathyroids were found *post mortem*.

2. It is suggested that the impetus for the secondary parathyroid hyperplasia and hypersecretion is the phosphate retention, and that the demineralization of the skeleton in renal rickets is due, among other factors, to the necessity of excreting the retained phosphate as the insoluble salt of calcium in the bowel, to the compensatory secretion of increased amounts of parathyroid hormone, and possibly also to the chronic acidosis.

3. The underlying cause of the renal impairment in this patient was a bilateral hydronephrosis, probably the result of an obstruction in the genito-urinary tract.

4. The clinical symptomatology, the x-ray appearance of the bones, the metabolism of calcium and phosphorus, and even the presence of increased amounts of parathyroid hormone in the blood in the case described were indistinguishable from those seen in osteitis fibrosa of the osteoporotic type, complicated by impairment of renal function. The differential diagnosis between the two diseases rests largely on a chronological history as to the onset of renal failure, on the presence or absence of nephrolithiasis or nephrocalcinosis (present in hyperparathyroidism and absent in renal rickets), and on the presence or absence of congenital anomalies of the genito-ruinary tract.

5. Attention is also called to the use of the Hamilton and Schwartz test as a means of detecting increased amounts of parathyroid hormone in the blood in patients suspected of having parathyroid hypersecretion.

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